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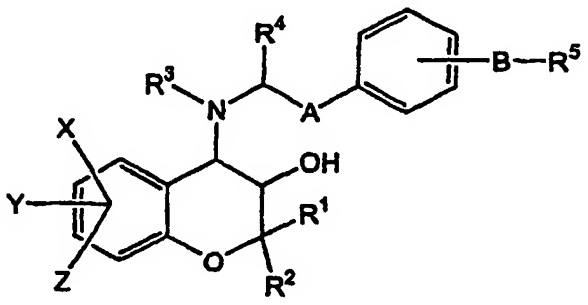
(54) Title: NOVEL BENZOPYRAN COMPOUNDS AND PROCESS FOR THEIR PREPARATION AND USE



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(57) Abstract: Novel benzopyran compounds that are useful as beta 3-adrenergic receptor agonists, pharmaceutical compositions containing these compounds, and processes for their preparation and use.

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NOVEL BENZOPYRAN COMPOUNDS AND PROCESS FOR THEIR PREPARATION AND USE

The present invention relates to novel benzopyran compounds. The invention also relates to the analogs, the tautomers, the regioisomers, the stereoisomers, the geometrical isomers, the polymorphs, the pharmaceutically acceptable salts, the pharmaceutically acceptable solvates of the novel benzopyrans and the pharmaceutical compositions containing them. The benzopyrans of the present invention are particularly potent β3-adrenergic receptor stimulating agents with excellent adrenoceptor selectivity, therefore they are useful in the prophylaxis or treatment of obesity, hyperglycemia, or diabetes mellitus. The compounds of the present invention are also useful in the treatment of asthma, inflammatory, cardiovascular, depression, prostate disorders, urinary continence, dyslipidemia, gastrointestinal motility disorders, peptic ulcer, ulcerative colitis, Crohn's disease, cough, angiogenesis and viral disease. Accordingly the compounds of the present invention are useful as β3-ardrenoceptor agonist.

The present invention also relates to a process for the preparation of the above said novel compounds of the formula **(I)** as defined below and a process for using the same.

The current preferred treatment for Type II, non-insulin dependent diabetes as well as obesity is diet and exercise, with a view toward weight reduction and improved insulin sensitivity. Patient compliance, however, is usually poor. The problem is compounded by the fact that there are currently no approved medications that adequately treat either type II diabetes or obesity. The invention described herein is directed toward an effective and timely treatment for these serious diseases.

One therapeutic opportunity that has been recognized involves the relationship between adrenergic receptor stimulation and anti-hyperglycemic effects. Compounds which act as β3 receptor agonists have been shown to exhibit a marked effect on lipolysis, thermogenesis and serum glucose levels in animal models of type II (non-insulin dependent) diabetes.

The β3 receptor, which is found in several types of human tissue including human fat tissue, has roughly 50 % homology to the β1 and β2 receptor subtypes yet is considerably less abundant. The importance of the β3 receptor is a relatively recent discovery since the amino acid sequence of the human receptor was only elucidated in the late 1980's. A large number of publications have appeared in recent years reporting

success in discovery of agents that stimulate the β3 receptor. Despite these recent developments, there remains a need to develop a selective β3 receptor agonist, which has minimal agonist activity against the β1 and β2 receptors.

The present invention provides compounds, which are selective β3 receptor agonists. As such, the compounds effectively lead to an increase in insulin sensitivity and are useful in treating type II diabetes and other ailments implicated by the β3 receptor.

Heredity, genetic disorders, tumors and hypothalmic disorders are among the many factors, which lead to the development of obesity. The hypothalamus plays a crucial role in appetite and metabolism, hence regulates adiposity. Traditional drug therapies seek to reduce food intake by reduction of appetite through CNS influences. However newer therapies will attempt to increase metabolism (thermogenesis) or reduce absorption of nutrients.

Thermogenesis, the major function of brown adipose tissue, is initiated by synaptic release of norepinephrine predominantly via β3- adrenergic receptor (β3-AR) to cause increased lipolysis. Hence β3-AR agonists may be useful as anti-obesity agents, and may also show anti-diabetic activity as well as this has generated immense interest in designing of very selective β3-AR agonists for the treatment of obesity and non-insulin dependent diabetes. They have fewer unwanted side effects than the 'absorption agents' and the 'appetite reducing agents'. Recent reports of missense mutation in the coding region of the β3-AR gene resulting in the substitution of tryptophan to arginine at codon 64 (Trp64Arg) and its association with the moderate obesity has further convinced the researchers to look for a novel target towards the therapy of obesity.

It is clear that the β3 AR plays a key role in mediating thermogenesis in rodents, and that specific β3 AR agonists increase metabolic rate and lead to weight loss in obese rodents, the role β3 ARs in humans remains controversial. In human newborn perirenal brown adipose tissue (BAT), the levels of β1, β2 and β3 mRNA were found to be 28, 63, 9% respectively, of the total adrenergic receptor mRNA; however, in adult human abdominal white adipose tissue (WAT), no β3 mRNA was detected by Northern blot analysis. In a separate study, using a sensitive and specific Rnase protection assay without previous PCR amplication, β3 mRNA was detected in human WAT, gall bladder, and small intestine, confirming earlier reports. It was also found to a lesser extent in

stomach and prostate, but was absent in cerebral cortex, cerebellum, liver, pancreas, gastrocnemius and soleus muscle, left ventricle, lung corpus cavernosa and kidney.

The β3 AR appears to play a key role in the action and regulation of leptin. This hormone, the product of the ob gene, is secreted by adipocytes and, acting via the hypothalamous, inhibits food intake and stimulates metabolic rate. Leptin-induced activation of the sympathetic nervous system and the resultant β3 AR-mediated thermogenesis in BAT may be responsible for the latter effect.

The present invention provides compounds, which are selective β3 receptor agonists. As such, the compounds effectively lead to an increase in insulin sensitivity and are useful in treating type II diabetes and other ailments implicated by the β3 receptor.

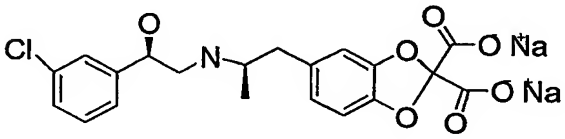
β3- Adrenoceptor agonists were found to have remarkable anti-obesity and anti-diabetic effects in rodents shortly after their discovery in the early 1980s. Despite these promising qualities, several pharmaceutical problems and theoretical concerns have slowed the development of these products as therapeutic agents in humans during the last 15 years. Pharmaceutical problems in this area concern important differences between Rodent & Human β3-AR and the difficulty in finding compounds with sufficient bioavailability and a highly selective and full agonist at the human receptor. Some of these problems seem to have been solved with the cloning of the Human β3-AR, which has made it possible to develop novel compounds directly and specifically against the human receptor. Recent studies using CL-316243, a highly selective β3-Adrenergic compound, have provided new insights into the potential mechanisms of action of these drugs in Rodents as well as in Humans. It appears that chronic β3-adrenergic stimulation in white adipose tissue increases the expression of newly discovered mitochondrial uncoupling proteins (UCP 2 & 3) and a "reawakening" of dormant brown adipocytes. In addition, β3-ARs may be present in skeletal muscle where ectopic expression of UCP-1 has been reported (Weyer.C et.al., Diabetes Metab., 1999, **25**, 11-21). If these findings are confirmed, tissues other than brown fat may play an important role in mediating β3-adrenergic effects on thermogenesis and substrate oxidation.

Medical treatment of obesity becomes a necessity when prevention fails. Any strategic medicinal development must recognize that obesity is a chronic, stigmatized and costly disease that is increasing in prevalence. Since obesity can rarely

be cured, treatment strategies are effective only as long as they are used. For a drug to have significant impact on body weight it must ultimately reduce energy intake, increase energy expenditure, or both. Currently approved drugs for long-term treatment of obesity include sibutramine, which inhibits food intake, and orlistat, which blocks fat digestion.

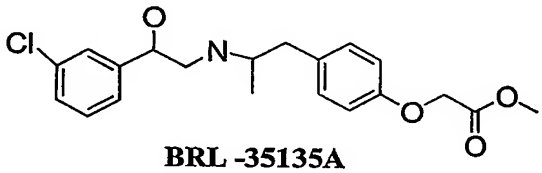
There are two main classes of compounds, which are known to bind with high affinity to β3 ARs, the aryoloxypropanolamines and the arylethanolamines. Interest in the former class of compounds, which are typically beta blockers, stems from the fact that aryloxypropanolamine (J.R.S.Arch et.al., Nature, , 1984, **309,** 163) a β1/β2 AR antagonist, has partial agonist activity at the human β3 AR (F.LÖnnqvist et.al., Br.J.Pharm.,1993, **110,** 929)

Although several research groups all over the world are working in this direction for achieving the desired highly selective β3 adrenoceptor agonists, so far the success is limited. Among the various compounds which showed potent β3 adrenoceptor agonists are listed below:



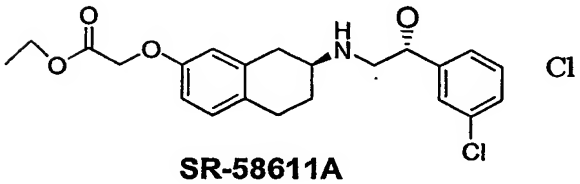
BTA-243

(2)



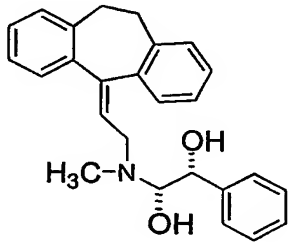
BRL -35135A

(3)



SR-58611A

(4)

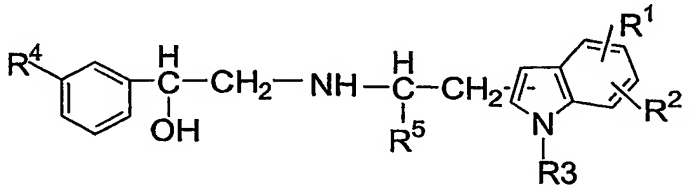


WAS- 4304

(5)

"BTA-243" of the formula (2) (Smith Kline Beecham's compound) has reached the completion stage of Phase-II clinical trials. BRL-35135A of the formula (3) (SmithKline Beecham's phase -II) SR-58611A of the formula (4) and (Sanofi's Phase -II), WAS-4304 of the formula (5) (Sanofi-Synthelabo's preclinical) have also shown β3-AR activity.

During the course of research aimed at the development of novel antidiabetic compounds having β3-adrenergic receptor agonists, we have found in the literature a number of publications, which are discussed below and hereby incorporated herein by reference. European publication EP 0801059 dated October 15, 1997 discloses selective β3 agonists of the formula (6)



(6)

wherein R^1 is lower alkoxy, lower alkoxy carbonyl-lower alkoxy, carboxy lower alkoxy, lower alkoxy carbonyl, phenyl lower alkoxy, lower alkyl being optionally substituted by hydroxy , di-lower alkylaminosulfonyl, etc.,

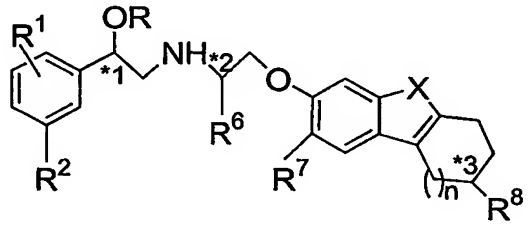
R^2 is hydrogen, halogen, lower alkoxy, lower alkoxy carbonyl-lower alkoxy, carboxy-lower alkoxy, etc.;

R^3 is hydrogen or lower alkyl;

R^4 is halogen or trifluoromethyl; and

R^5 is lower alkyl.

European publication EP 0997458 dated January 14, 1999 discloses beta-3 adrenoceptor agonist, prevents diabetes, obesity, hyperlipemia of the formula (7)



(7)

wherein R represents hydrogen or methyl;

R^1 represents hydrogen, halogeno, hydroxy, benzyloxy, amino or hydroxymethyl;

R^2 represents hydrogen, hydroxymethyl, NHR^3, $SO_2NR^4R^{4'}$, or nitro (wherein R^3 represents hydrogen, methyl, SO_2R^5, formyl, or $CONHR^{6'}$; R^5 represents lower alkyl, benzyl or $NR^4R^{4'}$; R^4 and $R^{4'}$ may be the same or different and each other represents hydrogen, lower alkyl or benzyl; and $R^{6'}$ represents hydrogen or lower alkyl);

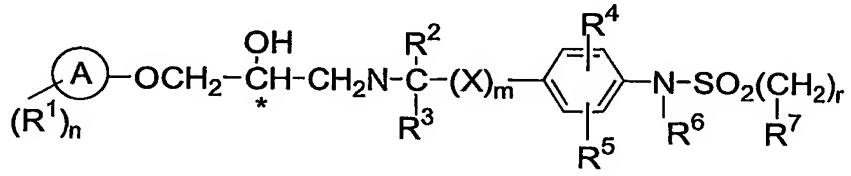
R^6 represents hydrogen or lower alkyl;

n is 1 or 2;

X represents secondary nitrogen, oxygen or sulfur; and when n is 1 , then one of R^7; and

R^8 represents hydrogen while another represents hydrogen, amino, acetylamino or hydroxy, or when n is 2, then R^8 represents hydrogen while R^7 represents hydrogen, amino, acetylamino, or hydroxy.

U.S. Patent 5,451,677 granted on September 19, 1995 discloses selective beta-3 adrenergic receptor agonists of the formula **(8).**



(8)

where

n is 0 to 7;

m is 0 or 1;

r is 0 to 3;

A is phenyl, naphthyl, a 5 or 6 membered heterocyclic ring with from 1 to 4 hetero atoms selected from oxygen, sulfur or nitrogen, a benzene ring fused to a C_3-C_8 cycloalkyl ring, a benzene ring fused to a 5 or 6 membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen or a 5 or 6 membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen fused to a 5 or 6 membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^1 is hydroxy, oxo, halogen, cyano, nitro, NR^8R^8, SR^8, trifluoromethyl,C_1-C_6 alkyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl, phenyl, SO_2R^9, NR^8COR^9, COR^9, $NR^8SO_2R^9$, $NR^8CO_2R^8$ or C1-C6 alkyl substituted by hydroxy, nitro, halogen, cyano,NR^8R^8, SR^8, trifluoromethyl, C_1-C_6 alkoxy, C_3-C_8 cycloalkyl phenyl, SO_2R^9, NR^8COR^9, COR^9, $NR^8CO_2R^8$, $NR^8SO_2R^9$ or R1 is a 5 or 6-membered heterocycle with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^2 and R^3 are independently hydrogen, C_1-C_6 alkyl, or C_1-C_6 alkyl substituted by 1 to 3 of hydroxy, C_1-C_6 alkoxy, or halogen;

X is $-CH_2-$,$-CH_2CH_2-$, -CH=CH-,or $-CH_2O-$;

R^4 and R^5 are independently hydrogen, C_1-C_6 alkyl, halogen, NHR^8, OR^8, SO_2R^9 or $NHSO_2R^9$;

R^6 is hydrogen or C_1-C_6 alkyl;

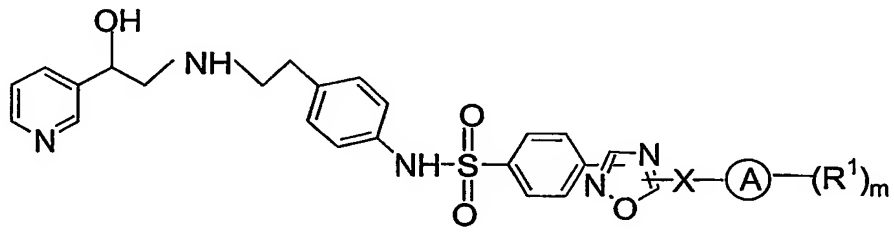
R^7 is C_1-C_6 alkyl, C_3-C_8 cycloalkyl, or B-$(RI)_n$;

B is phenyl, naphthyl, a 5 or 6 membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur or nitrogen, a benzene ring fused to a C_3-C_8 cycloalkyl ring, a benzene ring fused to a 5 or 6 membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen or a 5 or 6 membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen fused to a 5 or 6 membered heterocyclic ring with from 1 to 3 heteroatoms selected from oxygen, sulfur or nitrogen;

R^8 is hydrogen, C_1-C_{10} alkyl, C_3-C_8 cycloalkyl, phenyl optionally substituted by 1 to 3 of halogen, C_1-C_6 alkyl or alkoxy, or C_1-C_{10} alkyl substituted by 1 to 3 hydroxy, halogen, CO_2H, CO_2-C_1-C_6alkyl,C_3-C_8 cycloalkyl, C_1-C_6alkoxy, or phenyl optionally substituted by from 1 to 3 of halogen, C_1-C_6 alkyl or C_1-C_6 alkoxy; and

R^9 is R^8, NHR^8, NR^8R^8.

U.S. Patent 6,034,106 granted on March 07, 2000 discloses oxadiazole substituted benzenesulfonamides, which are useful as antiobesity and antidiabetic compounds of the formula **(9)**.



(9)

wherein

X is

(1) a bond,

(2) C_1-C_3 alkylene optionally substituted with 1 or 2 groups selected from methyl, C_1-C_5 alkoxy, hydroxy, and halogen

(3) C_1-C_3 alkylene optionally substituted with 1 or 2 groups selected from methyl, C_1-C_5 alkoxy, hydroxy, and halogen wherein said alkylene contains up to two groups selected from Q and carbonyl,

(4) Carbonyl, or

(5) Q

m is 0 to 5;

A is

(1) phenyl,

(2) a 5 or 6 membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur, and nitrogen,

(3) a benzene ring fused to a C_5-C_{10} carbocyclic ring,

(4) a 5 or 6 membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur, and nitrogen fused to a 5 or 6 membered heterocyclic ring from 1 to 4 heteroatoms selected from oxygen, sulfur, and nitrogen

(5) a 5 or 6 membered heterocyclic ring with from 1 to 4 heteroatoms selected from oxygen, sulfur, and nitrogen fused to a C_5-C_{10} carbocyclic ring;

R^1 is

(1) C_1-C_{10} alkyl optionally substituted with up to 5 groups selected from

(a) hydroxy,

(b) halogen,

(c) cyano,

(d) QR^2

(e) C_3-C_8 cycloalkyl,

(f) A optionally substituted with up to 5 groups selected from halogen, C_1-C_{10} alkyl and C_1-C_{10} alkoxy,

(g) $Q'COR^3$,

(h) $S(O)_nR^3$, where n is 0 to 2,

(i) $NR^2SO_2R^3$,

(j) $NR^2CO_2R^2$, and,

(k) CO_2R^2

(2) C_3-C_8 cycloalkyl,

(3) oxo,

(4) halogen,

(5) cyano,

(6) QR_2,

(7) $S(O)_nR^3$, where n is 0 to 2,

(8) $Q'COR^3$,

(9) $NR^2SO_2R^3$,

(10) $NR^2CO_2R^2$

(11) A optionally substituted with up to 5 groups independently selected from

(a) R^2

(b) QR^2

(c) Halogen, and

(d) Oxo; or

(12) CO_2R^2;

R^2 is

(1) hydrogen,

(2) C_1-C_{10} alkyl optionally substituted with up to 5 groups selected from

(a) hydroxy,

(b) halogen,

(c) CO_2R^4,

(d) $S(O)_n$-C_1-C_{10}alkyl, where n is 0 to 2,

(e) C_3-C_8 cycloalkyl,

(f) C_1-C_{10} alkoxy, and

(g) A optionally substituted with up to 5 groups selected from halogen, C_1-C_{10} alkyl,C_1-C_{10} alkoxy,

(3) C_3-C_8 cycloalkyl, or

(4) A optionally substituted with up to 5 groups selected from

(a) halogen,

(b) nitro,

(c) oxo,

(d) NR^4R^4,

(e) C_1-C_{10} alkoxy,

(f) $S(O)_n$-C_1-C_{10}alkyl, where n is 0 to 2, and

(g) C_1-C_{10} alkyl optionally substituted with up to 5 groups selected from hydroxy, halogen, CO_2R^4, $S(O)_n$-C_1-C_{10}alkyl, where n is 0 to 2, C_3-C_8 cycloalkyl, C_1-C_{10} alkoxy, and A optionally substituted with up to 5 groups selected from halogen, C_1-C_{10} alkyl, C_1-C_{10} alkoxy;

R^3 is

(1) R^2 or

(2) NR^2R^2;

R^4 is

(1) H, or

(2) (2) C_1-C_{10} alkyl;

Q is

(1) $N(R^2)$,

(2) O or,

(3) $S(O)_n$ and n is 0 to 2;

Q' is

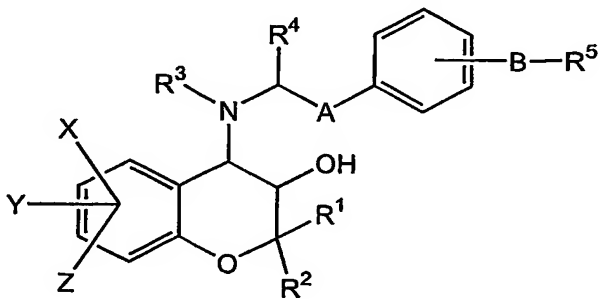
(1) $N(R^2)$,

(2) O or

(3) A bond.

Recognizing the importance of development of highly selective β3 adrenoceptor agonists we continued our research work towards achieving the above objectives and arrived at the invention described herein.

The present invention provides novel benzopyrans of the general formula (1)



(1)

wherein X, Y and Z independently may be the same or different and represent hydrogen, hydroxy, carboxyl, cyano, amino, nitro, halogen, formyl, oxo (=O), haloalkyl, cycloalkylalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic ring or -COR, -COOR, $-C(O)NRR^y$, $-NRR^y$, $-NRSO_2R^y$, $-NRS(O)R^y$, -OR, -OCOR, $-OC(O)R-$, $-OCONRR^y$, -ROR, -RCOOR, $-RC(O)NRR^y$, -RCOR, -RCS, -SR, -SOR, $-SO_2R$, $-SO_2NRR^Y$, $-SONRR^Y$ (wherein R, R^y or R^z in each of the above groups can be hydrogen, alkyl, aryl, cycloalkyl, arylalkyl, heterocyclic ring); or

Y and Z together form a 5 to 7 membered saturated, partly unsaturated or aromatic carbocyclic ring or heterocyclic ring having up to 2 hetero atoms selected from the series comprising S, N and O and which are optionally substituted by identical or different substituents selected from the group comprising straight chain or branched alkyl and alkoxy having in each case up to 6 carbon atoms, hydroxyl, cycloalkyl having 3-7 carbon atoms, phenyl, halogen, cyano, oxo (C=O) and nitro;

wherein R^1 and R^2 may independently be the same or different and represent hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or R^1 and R^2 together with a carbon atom to which they are attached form a 5-7 membered carbocyclic ring;

wherein R^3 is hydrogen, substituted or unsubstituted alkyl, alkoxycarbonyl, benzyl, or benzyloxycarbonyl;

wherein R^4 is hydrogen, substituted or unsubstituted alkyl, hydroxy alkyl, alkoxyalkyl or haloalkyl ; R^4 and benzene may optionally together with a carbon atom to which they are attached form a carbocyclic ring;

wherein A is $-(CH_2)_n-$, in which n is 0, 1,2 or 3;

wherein B is chemical bond, –O- or $N(R^6)$;

wherein R^6 may be hydrogen , substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl;

wherein R^5 may be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl or substituted or unsubstituted heterocyclic ring, $-RCOOR^x$, $-SO_2R$, $-CONHSO_2R$, -C(O)NHR, -C(S)NHR, -COOR, -C(O)R, -ROH, $-RCONH_2$, -RCONHOH, $-R(COOH)_2$, $-RSO_3H$

(wherein R and R^x in each of the above groups can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted heterocyclic ring);

and their analogs, the tautomers, the regioisomers, the stereoisomers, the geometrical isomers, the polymorphs, the pharmaceutically acceptable salts, the pharmaceutically acceptable solvates which are useful in the prophylaxis or treatment of obesity, hyperglycemia, or diabetes mellitus.

According to another feature of the present invention there are provided pharmaceutical compositions containing the novel benzopyrans and the analogs, the tautomers, the regioisomers, the stereoisomers, the geometrical isomers, the polymorphs, the pharmaceutically acceptable salts, the pharmaceutically acceptable solvates of the benzopyrans of formula (1).

The pharmaceutical composition may also contain one or more other clinically useful antidiabetic agents.

According to another feature of the present invention there is provided a process for the preparation of the novel benzopyrans of the general formula (1) their analogs, the tautomers, the regioisomers, the stereoisomers, the geometrical isomers, the polymorphs, the pharmaceutically acceptable salts, the pharmaceutically acceptable solvates thereof.

According to a further feature of the invention, there is provided a method for stimulating metabolic activity in a patient to be treated comprising administering to the patient the compound of formula (1) in an amount effective for such stimulation. There is also provided a method for increasing sensitivity of a patient to insulin comprising administering to the patient the compound of formula (1) in an amount effective to increase such sensitivity.

The term 'alkyl' as used herein refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing solely of carbon and hydrogen atoms, containing no unsaturation, having from one to six carbon atoms, and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, n-propyl, 1-methylethyl (isopropyl), n-butyl, n-pentyl, 1,1-dimethylethyl (t-butyl), and the like.

The term 'alkoxy' refers to a radical of the formula $-OR_a$ where R_a is an alkyl radical as defined above, e.g., methoxy, ethoxy, propoxy and the like.

The term "alkynyl" refers to straight or branched chain hydrocarbyl radicals having at least one carbon-carbon triple bond, and having in the range of about 2 up to 12 carbon atoms (with radicals having in the range of about 2 up to 10 carbon atoms presently being preferred) e.g., ethynyl, propynyl, butnyl and the like.

The term "cycloalkyl" refers to cyclic ring-containing radicals containing in the range of about 3 up to 8 carbon atoms such as cyclopropyl, cyclobuyl, cyclopentyl, cyclohexyl and the like.

The term "carbocyclic" refers to an cyclic group containing 3-10 carbon atoms.

The term "Alkenyl" refers to aliphatic hydrocarbon group containing a carbon-carbon double bond and which may be a straight or branched or branched chain having about 2 to about 10 carbon atoms in the e.g., ethenyl, 1-propenyl, 2-propenyl (allyl), iso-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.

The term "aryl" refers to aromatic radicals having in the range of 6 up to 14 carbon atoms such as phenyl, naphthyl, tetrahydronapthyl, indanyl, biphenyl and the like.

The term "arylalkyl" refers to an alkyl group as defined above bonded to an aryl group as defined above. e.g., $-CH_2C_6H_5$, $C_2H_5C_6H_5$ and the like.

The term "Heterocyclic ring" refers to a stable 3- to 15 membered ring radical which consists of carbon atoms and from one to five heteroatoms selected from the group consisting of nitrogen, phosphorus, oxygen and sulfur. For purposes of this invention, the heterocyclic ring radical may be a monocyclic, bicyclic or tricyclic ring system, which may include fused or bridged ring systems, and the nitrogen, phosphorus, carbon oxygen or sulfur atoms in the heterocyclic ring radical may be optionally oxidized to various oxidation states. In addition, the nitrogen atom may be optionally quaternized; and the ring radical may be partially or fully saturated or aromatic. Examples of such heterocyclic ring radicals include, but are not limited to, azetidinyl, acridinyl, benzodioxolyl, benzodioxanyl, benzofurnyl, carbazolyl, cinnolinyl, dioxolanyl, indolizinyl, naphthyridinyl, perhydroazepinyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pyridyl pteridinyl, purinyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrazoyl, imidazolyl, tetrahydroisouinolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, 2-oxoazepinyl, azepinyl, pyrrolyl, 4-piperidonyl, pyrrolidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolinyl,

oxasolidinyl, triazolyl, indanyl, isoxazolyl, isoxasolidinyl, morpholinyl, thiazolyl, thiazolinyl, thiazolidinyl, isothiazolyl, quinuclidinyl, isothiazolidinyl, indolyl, isoindolyl, indolinyl, isoindolinyl, octahydroindolyl, octahydroisoindolyl, quinolyl, isoquinolyl, decahydroisoquinolyl, benzimidazolyl, thiadiazolyl, benzopyranyl, benzothiazolyl, benzooxazolyl, furyl, tetrahydrofurtyl, tetrahydropyranyl, thienyl, benzothienyl, thiamorpholinyl, thiamorpholinyl sulfoxide thiamorpholinyl sulfone, dioxaphospholanyl and oxadiazolyl and the like.

The term "Heteroaryl" refers to heterocyclic ring radical as defined above. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "Heterocyclyl" refers to a heterocylic ring radical as defined above. The heteroaryl ring radical may be attached to the main structure at any heteroatom or carbon atom that results in the creation of a stable structure.

The term "Halogen" refers to radicals of Fluorine, Chlorine, Bromine, and Iodine.

The substituents in the 'substituted alkyl', 'substituted alkenyl' 'substituted alkynyl', 'substituted arylalkyl' 'substituted cycloalkyl', may be the same or different which are selected from the groups such as hydrogen, hydroxy, halogen, halolkyl, carboxyl, cyano, amino, nitro, oxo(=O), azido, formyl, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, alkylaryl, arylalkyl, aryl, aroyl, heterocyclic ring or –COOR,-C(O)R, -C(S)R, -C(O)NRR^y, -C(O)ONRR^y, -NRCONR^{y}R^z, -N(R)SOR^y, -N(R)SO$_2$R^y, -N(R)CO-, -(=N-N(R)R^y), -N(R)R^{y}CO-, -NRR^{y}C(O)OR^z, -NRR^y, -NRC(O)R^y-, -NRC(S)R^y -, -NRC(S)NR^{y}R^z, -N(R)SO-, -NRSO$_2$-, -OR, -ORC(O)NR^{y}R^z, -ORC(O)OR^y-, -OC(O)R, -OC(S)R-, -OC(O)OR-, -OC(O)NRR^y, -RNR^{y}R^z, -RR^{y}R^z, -RCF$_3$, -RNR^{y}C(O)R^z, -ROR^y, -RC(O)OR^y, -RC(O)NR^{y}R^z, -RCS, -RC(O)R, -ROC(O)R^y, -SR, -SOR, -SO$_2$R, -SO$_3$R, -ONO$_2$,(wherein R,R^y and R^z in each of the above groups can be hydrogen atom, alkyl, haloalkyl, alkylaryl, arylalkyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclic ring).

The substituents in the 'substituted aryl', 'substituted heterocyclic ring' may be the same or different which are selected from the groups such as hydrogen, hydroxy, halogen, halolkyl, carboxyl, cyano, amino, nitro, oxo(=O), azido, formyl, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, alkylaryl, arylalkyl, aryl, aroyl, heterocyclic ring or –COOR,-C(O)R, -C(S)R, -C(O)NRRy, -C(O)ONRRy, -

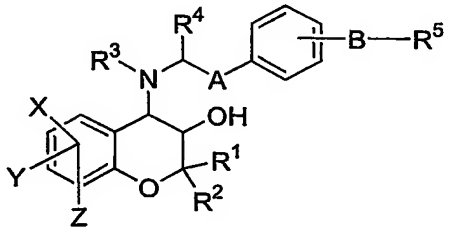
NRCONRyRz, -N(R)SORy, -N(R)SO2Ry, -N(R)CO-, -(=N-N(R)Ry), -N(R)RyCO-, -NRRyC(O)ORz, -NRRy, -NRC(O)Ry-, -NRC(S)Ry -, -NRC(S)NRyRz, -N(R)SO-, -NRSO2-, -OR, -ORC(O)NRyRz, -ORC(O)ORy-, -OC(O)R, -OC(S)R-, -OC(O)OR-, -OC(O)NRRy, -RNRyRz, -RRyRz, -RCF3, -RNRyC(O)Rz, -RORy, -RC(O)ORy, -RC(O)NRyRz, -RCS, -RC(O)R, -ROC(O)Ry, -SR, -SOR, -SO2R, -SO3R, -ONO2,(wherein R,Ry and Rz in each of the above groups can be hydrogen atom, alkyl, haloalkyl, alkylaryl, arylalkyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclic ring)

The term "Pharmaceutically acceptable salts" means non-toxic salts of the compounds of this invention which are generally prepared by reacting the free base / acid with a suitable organic or inorganic acid/base. Representative salts include acetate, ascorbate, sodium, potassium, Tris, benzenesulfonate, benzoate, bicarbonate, borate, bromide, calcium edetate, carbonate, chloride, citrate, dihydrochloride, edetate, mesylate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxyapthoate, iodide, isothionate, α-ketoglutarate, α-glycerophosphate, glucose-1 phosphate lutarate lactate, lactobionate, laurate, malate, methane-sulphate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmaote, palmitate, panthothenate, phosphate/diphosphate, polygalacturonate, salicylate, sterate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide, valerate.

It will be appreciated that some of the compounds according to the invention can contain one or more asymmetrically substituted carbon atom. The presence of one or more of these asymmetric centers in compounds of formula **(1)** can give rise to stereoisomers and in each case the invention is to be understood to extend to all such stereoisomers, including enantiomers and diastereoisomers and their mixtures, including racemic mixtures. The invention may also contain E and Z geometrical isomers wherever possible in the compounds of general formula **(1)**, which includes the single isomer, or mixture of both of the isomers.

The invention also envisages within its scope the polymorphs and the analogs of the compounds of the general formula **(1)** as defined above.

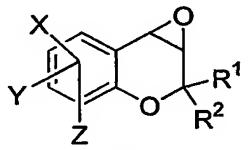
Accordingly the present invention provides a process for the preparation of compounds of the general formula (**1**)



1

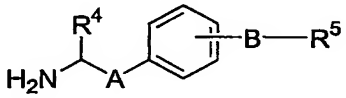
wherein all the symbols have the meanings given earlier which comprises

(a) reacting the compounds of the general formula (**10**)



10

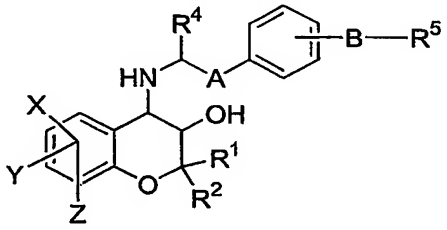
wherein all the symbols have the meanings given earlier with compounds of the formula (**11**)



11

or a salt thereof

wherein all the symbols have the meanings given earlier by conventional method to obtain the compound with general formula (**1a**)



1a

wherein all the symbols have the meanings given above; and if desired

(b) reacting the compounds of the general formula **1a** with the compound of general formula **12**

P-R_3

where P represents halogen such as Cl or Br and R3 has the meaning given above or P-R_3 is amino protecting reagent

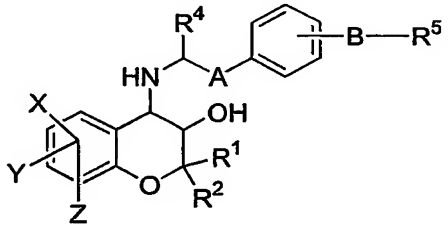
to obtain the compound of general formula **1;**

(c) converting the resulting compounds of the general formula **(1)** wherein all the symbols have the meanings given above into their analogs, their tautomers, their regioisomers, their stereoisomers, their geometrical isomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates by conventional methods; and if desired

(d) further purifying the resulting compounds by conventional methods.

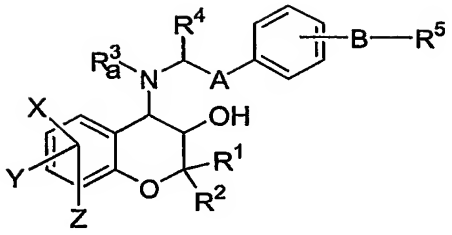
In a preferred embodiment of the invention the reaction to synthesize compound **1a** may be carried out in the presence of a base for example a trialkylamine such as trimethylamine, triethylamine etc., an alkali metal carbonate such as sodium carbonate, potassium carbonate and the like, an alkaline earth metal carbonate such as magnesium carbonate, calcium carbonate and the like, an alkali metal bicarbonate such as sodium bicarbonate, potassium bicarbonate, and the like. The reaction is usually carried out in a solvent, such as methanol, ethanol, isopropanol, diethyl ether, THF, dioxane, or any other organic solvent, which does not adversely influence the reaction. Reaction can be carried out at 0-80°C, preferably 25- 80°C.

According to another feature of the invention there is provided a process for the preparation of the compounds of the general formula **(1a)** where B =O and R4 is H.



(1a)

from the compound of general formula **(1b)**



(1b)

comprising the steps of:

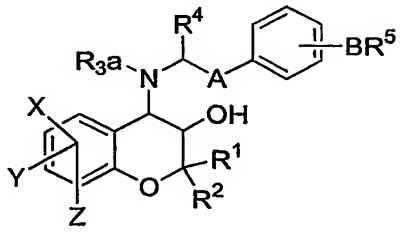
(a) deprotecting the amino protecting group wherein R3a represents an amino protecting group; and if desired

(b) converting the resulting compound of the general formula **(1a)**, wherein all the symbols have the meanings given above into their analogs, their tautomers, their regioisomers, their stereoisomers, their geometrical isomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, by conventional methods; and if desired

(c) further purifying the resulting compounds by conventional methods.

In a preferred embodiment of the invention the reaction may be carried out using conventional reaction by which amino protective group is removed. Alkoxycarbonyl protecting groups are removed in solvents such as DCM, methanol, ethyl acetate and acids such as HCl, TFA. The benzyloxy carbonyl and benzyl groups are removed in solvents such as methanol, ethanol, ethyl acetate, catalyst such as Pd/C and source of hydrogen such as hydrogen gas, ammonium formate, etc. The temperature range varies from 0 to 35°C.

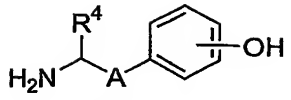
According to yet another feature of the invention there is provided a process for the preparation of the compounds of general formula **[1b]**



[1b]

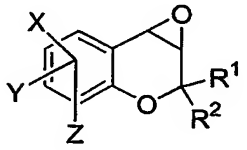
where all the symbols have the meanings given except that R4 is H and B is O, which comprises:

a) reacting the compounds of the general formula **13** or a salt thereof



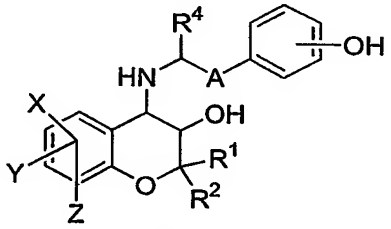
13

with the compounds of the general formula **10**



10

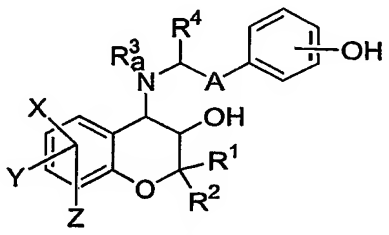
where R4 is H and all the symbols have the meanings given earlier to obtain the compounds of the general formula **14**



14

In a preferred embodiment of the invention the reaction may be carried out in the presence of a base, for example a trialkylamine such as trimethylamine, triethylamine and the like, an alkali metal carbonate such as sodium carbonate, potassium carbonate and the like, an alkaline earth metal carbonate such as magnesium carbonate, calcium carbonate and the like an alkali metal bicarbonate such as sodium bicarbonate, potassium bicarbonate, and the like. The reaction is usually carried out in a solvent, such as methanol, ethanol, isopropanol, diethyl ether, THF, dioxane, or any other organic solvent, which does not adversely influence the reaction. The reaction can be carried out at 0°C-80°C preferably 25°C-80°C.

(b) protecting the amino group present in the compound of the general formula **14** by conventional methods to obtain the compound with formula **14a**



14a

where R^{3a} is an amino protecting group and all the other symbols have the meanings given earlier.

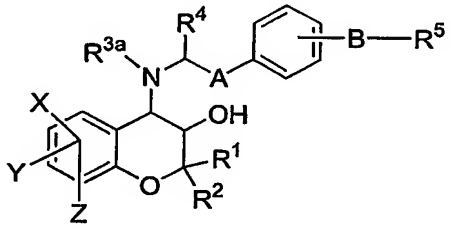
In a preferred embodiment of the invention the reaction may or may not be carried out in the presence of a base such as trialkylamine such as trimethylamine, triethylamine and the like, alkali metal carbonate such as sodium carbonate, potassium carbonate and the like, an alkaline earth metal carbonate such as magnesium carbonate, calcium carbonate and the like an alkali metal bicarbonate such as sodium bicarbonate, potassium bicarbonate, and the like. The reaction is usually carried out in a solvent, such as an diethyl ether, THF, dioxane, DCM, chloroform or any other organic solvent, which does not adversely influence the reaction. Reaction can be carried out under 0°C- 32°C

(c) reacting the resulting protected compounds of the general formula 14a with compounds of the general formula 15

$$Q\text{-}R^7$$

15

where Q represents halogens, sulphonylchloride, isocynate, isothiocyanate, sulphonyl isocyanate, acid chlorides, anhydrides and and R^7 is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted or unsubstituted alkylaryl, substituted or unsubstituted heterocycle, heteroalkyl to obtain the compound with general formula **1b** where R^{3a} is an amino protecting group and R4 =H, B = O.



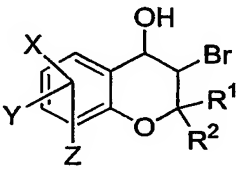
1b

In a preferred embodiment of the invention the reaction may or may not be carried out in the presence of a base such as trialkylamine such as trimethylamine, triethylamine and the like, alkali metal carbonate such as sodium carbonate, potassium carbonate and the like, an alkaline earth metal carbonate such as magnesium carbonate, calcium carbonate and the like an alkali metal bicarbonate such as sodium bicarbonate, potassium bicarbonate and the like. The reaction is usually carried out in a solvent such as diethylether,THF, acetone, dioxane, or any other organic solvent, which does not

adversely influence the reaction. Reaction can be carried out under 0°C- 50°C preferably 10°C- 40°C.

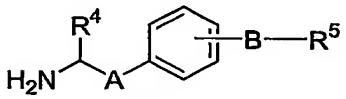
According to still another feature of the invention there is provided a process for the preparation of compounds of formula **[1a]** or a salt thereof wherein all the symbols have the meanings given earlier which comprises:

(a) reacting the compounds of the general formula **16**



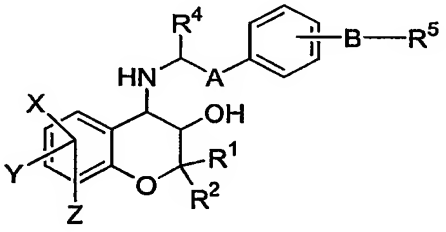
16

where all the symbols have the meanings given earlier with the compounds of the general formula **11** or a salt thereof



11

by conventional methods to obtain the compound of the general formula **1a;**



1a

and if desired

(b) further purifying the resulting compounds by conventional methods.

In a preferred embodiment of the invention the reaction may be carried out in the presence of a base such as trialkylamine such as trimethylamine, triethylamine and the like. The reaction is usually carried out in a solvent, such as methanol, ethanol, isopropanol, diethyl ether, THF, dioxane, or any other organic solvent, which does not adversely influence the reaction. Reaction can be carried out under 0°C- 80°C preferably 25°C-50°C.

According to yet another feature of the invention there is provided a pharmaceutical composition especially useful as a beta 3 adrenoceptor agonist

comprising one or more compounds of the general formula 1 or their analogs, their tautomers, their regioisomers, their stereoisomers, their enantiomers, their diasteromers, their geometrical isomers, their polymorphs, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, and a pharmaceutically acceptable carrier or excipient.

According to an embodiment of the invention the pharmaceutical composition of the present invention may contain other known drugs.

Some of the preferred compounds according to the present invention are specified below:

1) 4-Benzylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol . Hydrochloride

2) 3,4-Dihydro-2,2-dimethyl-4-(2-phenyl)ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride

3) 3,4-Dihydro-2,2-dimethyl-4-(2-(4-methoxy)phenyl)ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride

4) 3,4-Dihydro-2,2-dimethyl-4-(2-(4-(3-phenyl)urido)phenyl) ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride

5) 2-[4-[*N*-Boc-*N*-[-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyranyl]aminoethyl]phenoxy] acetic acid ethyl ester.Hydrochloride.

6) 3',4'-Dihydro-3'-hydroxy-4'-(2-(4-methoxy)phenyl) ethylaminospiro [cyclohexane-1,2'-[2*H*]-[1]-benzopyran]. Hydrochloride

7) 3',4'-Dihydro-3'-hydroxy-4'-(2-phenyl)ethylaminospiro [cyclohexane-1,2'-[2*H*]-[1]-benzopyran]. Hydrochloride

8) 4-[2-[4-Benzyloxyphenyl]-1-hydroxymethyl]ethylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol, hydrochloride

9) 3,4-Dihydro-2,2-dimethyl-4-(1-hydroxymethyl-2-phenyl) ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride

10) 3,4-Dihydro-2,2-dimethyl-4-(2-(4-(4-toluenesulphonylamino)) phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride

11) 3,4-Dihydro-2,2-dimethyl-4-[1-methoxymethyl-2-phenyl] ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride

12) 4-((4-(4-Benzyloxy)phenyl)-2-hydroxy-2-methyl)but-3-ylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol.

13) 3,4-Dihydro-2,2-dimethyl-4-(1-methoxymethyl-2-(4-methoxy) phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride.

14) 4-[2-[4-Benzyloxyphenyl]-1-methoxymethyl]ethylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol.Hydrochloride

15) 3,4-Dihydro-2,2-dimethyl-4-(2-(4-(1-pyrrolo) benzenesulphonylamino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride.

16) 3',4'-Dihydro-3'-hydroxy-4'-(2-(4-(4-toluenesulphonylamino)) phenyl)ethylaminospiro[cyclohexane-1,2'-[2H]-[1]-benzopyran].Hydrochloride

17) 3,4-Dihydro-2,2-dimethyl-4-(2-(4-(4-methoxy)benzamido) phenyl)ethylamino-2*H*-1-benzopyran-3-ol .Hydrochloride

18) 3,4-Dihydro-2,2-dimethyl-4-(2-(*N'*-methyl-4-toluenesulphonyl) amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride

19) 3,4-Dihydro-2,2-dimethyl-4-(2-(4-(4-nitro)benzenesulphonyl) amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.

20) 3',4'-Dihydro-3'-hydroxy-4'-(2-(4-methoxybenzamido) phenyl)ethylaminospiro [cyclohexane-1,2'-[2*H*]-[1]-benzopyran]. Hydrochloride

21) 6-Chloro-2,2-dimethyl-3,4-dihydro-4-(2-(4-(4-toluenesulphonylamino))phenyl)ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride.

22) 3,4-Dihydro-2,2-dimethyl-4-[[3-[4-methoxy]phenyl]prop-2-yl]amino-*2H*-1-benzopyran-3-ol. Hydrochloride.

23) 2-[4-[*N*-[7-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy] acetic acid ethyl ester.Hydrochloride.

24) 2-[4-[*N*-[7-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy] acetic acid.Hydrochloride.

25) 3,4-Dihydro-2,2-dimethyl-4-[2-[4-[4-[3-[hex-1-yl]]urido] benzenesulfonamido]phenyl]ethylamino- 2*H*-1-benzopyran-3,6-diol.

26) 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-(4-fluoro)benzamido) phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride.

27) 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-(4-bromo benzene sulphonyl amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol

28) Carbonic acid, phenylmethyl 4-(*N*-(7-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl) aminoethyl)phenyl ester.Hydrochloride.

29) 2-[4-[*N*-[6-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy] acetamide-*N*'-hex-1-yl.Hydrochloride.

30) 3,4-Dihydro-4-(2-(4-(4-fluoro)benzamido)phenyl)ethylamino)-2*H*-1-benzopyran-3-ol.Hydrochloride.

31) 3,4-Dihydro-2,2-dimethyl-6-methoxy-4-(2-(4-(4-toluenesulphonyl amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride.

32) 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-(4-toluene sulphonyl amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride.

33) 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-((4-(3-oct-1-yl)-2-oxo)imidazolidinyl) benzenesulphonylamino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride.

In general, the ethereal solvents used in the above described processes for the preparation of compounds of the formula (**1**) are selected from diethyl ether, 1,2-dimethoxyethane, tetrahydrofuran, diisopropyl ether, 1,4 dioxane and the like. The chlorinated solvent which may be employed may be selected from dichloromethane, 1,2-dichloroethane, chloroform, carbontetrachloride and the like. Aromatic solvents which may be employed include benzene and toluene. Alcoholic solvents which may be employed include methanol, ethanol, n-propanol, isopropanol, tert.butanol and the like. Aprotic solvents which may be employed include N,N-dimethylformamide, dimethyl sulfoxide, and the like.

In general, the reaction time to carry out the above described processes for the preparation of compounds of the formula **1** may be in the range of 0.5 hr to 48 hrs, preferably between 0.5 hr to 16 hrs.

In general, the compounds prepared in the above described processes are obtained in pure form by using well known techniques such as crystallization using solvents such as pentane, diethyl ether, isopropyl ether, chloroform, dichloromethane, ethyl acetate, acetone, methanol, ethanol, isopropanol, water or their combinations, or column chromatography using alumina or silica gel and eluting the column with solvents such as hexane, petroleum ether (pet.ether), chloroform, ethyl acetate, acetone, methanol or their combinations.

Various polymorphs of a compound of general formula **1** forming part of this invention may be prepared by crystallization of compound of formula **1** under different conditions. For example, using different solvents commonly used or their

mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The present invention also provides pharmaceutical compositions, containing compounds of the general formula (1), as defined above, their derivatives, their analogs, their tautomeric forms, their enantiomers, their diasteromers, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or their pharmaceutically acceptable solvates in combination with the usual pharmaceutically employed carriers, diluents and the like. The pharmaceutical compositions according to this invention can be used for the treatment of allergic disorders.

The pharmaceutical compositions of the invention may be in a form normally employed, such as tablets, capsules, powders, syrups, solutions, suspensions and the like and may contain flavorants, sweeteners etc. in suitable solid or liquid carriers or diluents, or in suitable sterile media to form injectable solutions or suspensions. The active compounds of the formula (1) will be present in such pharmaceutical compositions in the amounts sufficient to provide the desired dosage. Thus, for oral administration, the compounds of the formula 1 can be combined with a suitable solid, liquid carrier or diluent to form capsules, tablets, powders, syrups, solutions, suspensions and the like. The pharmaceutical compositions may, if desired, contain additional components such as flavorants, sweeteners, excipients and the like. For parenteral administration, the compounds of the formula 1 can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. For example, solutions in sesame or peanut oil, aqueous propylene glycol and the like can be used, as well as aqueous solutions of water-soluble pharmaceutically-acceptable acid addition salts or salts with base of the compounds of the formula 1. The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

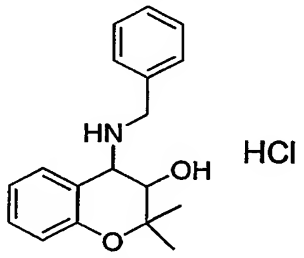
In addition to the compounds of formula (1) the pharmaceutical compositions of the present invention may also contain or be co-administered with one or more known drugs selected from other clinically useful anti diabetic agents.

The compounds of the formula (1) as defined above may be clinically administered to mammals, including human beings, via either oral or parenteral routes. Administration by the oral route is preferred, being more convenient and avoiding the possible pain and irritation of injection. However, in circumstances where the patient cannot swallow the medication, or absorption following oral administration is impaired, as by disease or other abnormality, it is essential that the drug be administered parenterally. However, the optimum dosage for the individual subject being treated will be determined by the person responsible for treatment, generally smaller doses being administered initially and thereafter increments made to determine the most suitable dosage.

The invention is explained in detail in the Examples given below which are provided by way of illustration only and therefore should not be construed to limit the scope of the invention.

EXAMPLE 1

Preparation of 4-benzylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol . Hydrochloride



Mixture of benzylamine (250 mg, 2.34 mM) and (±)-*trans*-3-bromo-2,2-dimethyl-3,4-dihydro-2*H*-1-benzopyran-4-ol (200 mg, 0.78mM) were heated together at 100°C for 4 hrs. Diethylether was added and the precipitated salt was filtered off. The filtrate was concentrated and purified by column chromatography to obtain the desired free amine, which was then dissolved in ethanolic HCl. Solvent was evaporated and the residue obtained was crystallized with chloroform/ether mixture to obtain the 4-benzylamino-3, 4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol with its HCl salt as a white solid.

Yield 0.052g, 20%., mp 239°C , HPLC purity > 95%.

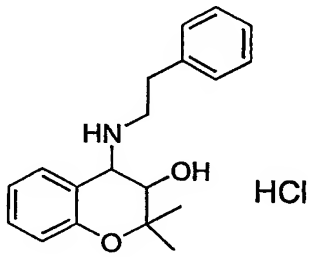
IR (KBr): 3338, 2936, 1584, 1492, 1459, 1308, 1264, 1147, 756, 693 cm^{-1}.

NMR ($CDCl_3$) δ: 1.08 (3H, s), 1.48 (3H, s), 3.73-3.79 (1H, m), 3.93-3.97 (2H, m), 4.94 (1H, d, J=7.14Hz), 6.89 (1H, d, J=8.05Hz), 7.03 (1H, m), 7.26-7.30 (3H, m), 7.42-7.43 (2H, m), 7.74 (1H, d, J=7.69Hz), 9.76 (1H, br s), 10.09 (1H, br s).

MS (M+H) calculated: 284.17, observed: 284.18.

EXAMPLE 2

Preparation of 3,4-dihydro-2,2-dimethyl-4-(2-phenyl)ethylamino-2*H*-1-benzopyran-3-ol, hydrochloride



Mixture of 2-phenethylamine (283 mg, 2.34 mM) and (±)-*trans*-3-bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ol (200 mg, 0.78mM) were heated together at 100°C for 4 hrs. Diethylether was added and the precipitated salt was filtered off. The filtrate was concentrated and purified by column chromatography to obtain the desired free amine, which was then dissolved in ethanolic HCl. Solvent was evaporated and the residue obtained was crystallized with chloroform/ether mixture to obtain the 3,4-dihydro-2,2-dimethyl-4-(2-phenyl)ethylamino-2*H*-1-benzopyran-3-ol, with its HCl salt as a white solid.

Yield 0.134g, 51%. mp 202-204°C, HPLC purity > 98%.

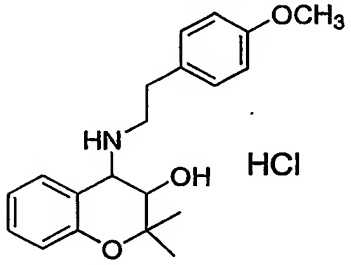
IR (KBr): 3256, 2715, 1583, 1492, 1459, 1369, 1308, 1251, 1086, 937, 759 cm^{-1}.

NMR ($CDCl_3$) δ: 1.16 (3H, s), 1.54 (3H, s), 2.86-3.38 (4H, m), 4.01-4.06 (1H, m), 4.79 (1H, d, J=8.42Hz), 5.39 (1H, d, J=4.4Hz), 6.85 (1H, d, J=7.69Hz), 7.01 (1H, m), 7.15-7.27 (5H, m), 7.61 (1H, d, J=8.06Hz), 9.87 (1H, br s).

MS (M+H) calculated: 298.18, observed: 298.19.

EXAMPLE 3

Preparation of 3,4-dihydro-2,2-dimethyl-4-(2-(4-methoxy)phenyl)ethylamino-2*H*-1-benzopyran-3-ol, hydrochloride



Mixture of (4-methoxy)-2-phenethylamine (2.037g, 13.47mM) and (±)-*trans*-3-bromo-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ol (1.15 g, 4.49 mM) were heated together at 120°C for 4 hrs. Diethylether was added and the precipitated salt was filtered off. The filtrate was concentrated and purified by column chromatography to obtain the desired free amine, which was then dissolved in ethanolic HCl. Solvent was evaporated and the residue obtained was crystallized with chloroform/ether mixture to obtain the 3,4-dihydro-2,2-dimethyl-4-(2-(4-methoxy)phenyl)ethylamino-2*H*-1-benzopyran-3-ol with its HCl salt as a white solid.

Yield 0.192g, 63%. mp 202-204°C, HPLC purity: > 98%.

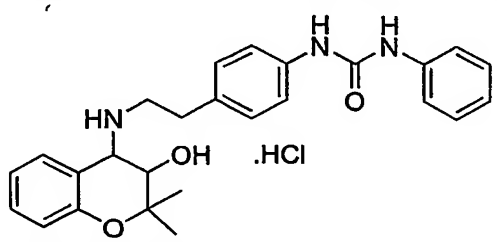
IR (KBr): 3337, 2975, 2934, 2609, 1613, 1585, 1515, 1493, 1461, 1251, 1180, 1060, 1036, 765 cm^{-1}.

NMR ($CDCl_3$): δ1.15 (3H, s), 1.53 (3H, s), 2.80 – 3.40 (4H, m), 3.74 (3H, s), 4.03 (1H, dd, J=4.5 & 8.7Hz), 4.78 (1H, d, J=8.6Hz), 5.49 (1H, d J=4.6Hz), 6.78 (2H, d, J=8.6Hz), 6.85 (1H, d, J=7.1Hz), 7.00 (1H, m), 7.07 (2H, d, J=8.6Hz), 7.25 (1H, t, J=7.1), 7.65 (1H, d, J=7.3Hz), 9.78 (1H, br s) and 9.91 (1H, br s).

MS (M+H) calculated: 328.19, observed: 328.20.

EXAMPLE 4

Preparation of 3,4-Dihydro-2,2-dimethyl-4-(2-(4-(3-phenyl)urido)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride



To a solution of 2-(4-(3-phenyl)urido)phenyl)ethylamine-hydrochloride (0.14g, 0.48 mM) in 0.4 ml methanol, was added triethylamine (0.36g, 3.56 mM). The reaction mixture was stirred for 20 minutes. To this was added 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.1g, 0.568 mM). Reaction mixture was stirred for 48 hrs at room temperature. The reaction mixture was evaporated and the residue obtained was reconstituted in ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. It was then evaporated and the resulting compound was purified on a silica gel column using $CHCl_3 \rightarrow 3\%MeOH/CHCl_3$ solvent system. It was then converted into its hydrochloride salt by dissolving it in ethanolic HCl and evaporating the solvent to obtain the desired product as a white solid.

Yield of 0.057g, 25%. mp164°C, HPLC purity > 99%.

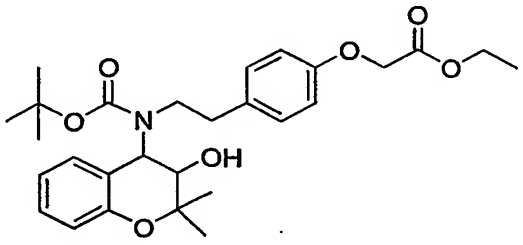
IR (Neat): 3293, 2774, 1667, 1596, 1548, 1498, 1459, 1443, 1311, 1233, 1145, 1074, 931, 754 cm^{-1}.

NMR ($CDCl_3$) δ: 1.21 (3H, s), 1.52 (3H, s), 2.75-3.00 (3H, m), 3.15 (1H, m), 3.96 (1H, br s), 4.46 (1H, m), 5.69 (1H, br s), 6.80-7.40 (12 H, m), 7.66 (1H, d, 6.9 Hz), 8.27 (1H, br s), 8.49 (1H, br s), 8.71 (1H, br s), 9.54 (1H, br s).

MS (M+H) Observed & calculated 432.2.

EXAMPLE 5

Preparation of 2-[4-[*N*-Boc-*N*-[-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy] acetic acid ethyl ester.Hydrochloride



To a solution of N-t-Boc 2,2-Dimethyl-3,4-dihydro-4-(2-(4-hydroxyphenyl)) ethylamino-2*H*-1-benzopyran-3-ol (0.5g, 1.21mM) and ethyl bromo acetate (0.242g, 1.452 mM) in 5 ml of acetone was added K_2CO_3 (0.2g, 1.452 mM). The reaction mixture was stirred for 18 hrs. The reaction mixture was filtered off. The filtrate was concentrated and the residue obtained was crystallized with pet ether to obtain the desired product as white solid.

Yield 0.501g, 82%. mp 85-88°C.

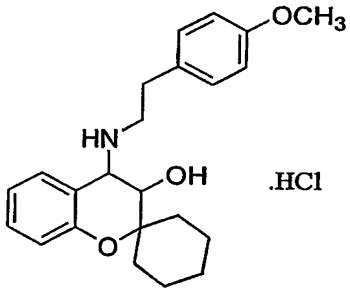
IR (Neat): 3391, 2978, 2936, 1753, 1674, 1513, 1488, 1456, 1195, 1182, 1088, 938, 811, 756 cm^{-1}.

NMR ($CDCl_3$) δ: 1.22 (3H, s), 1.28 (3H, t, 7 Hz), 1.47 (3H, s), 1.60 (9H, s), 2.50-3.00 (3H, m), 3.20 (1H, m), 3.56 (1H, d, 9.15 Hz), 4.25 (2H, q, 7 Hz), 4.56 (2H, s), 5.37 (1H, d, 9.8 Hz), 6.77-7.24 (8H, m).

MS (M+H) observed & calculated 500.3.

EXAMPLE 6

Preparation of 3',4'-dihydro-3'-hydroxy-4'-(2-(4-methoxy)phenyl)ethylaminospiro [cyclohexane-1,2'-[2*H*]-[1]-benzopyran]. Hydrochloride



Mixture of 2-(4-methoxy)phenethylamine (0.325g, 2.14mM) and 3'-bromo-3',4'-dihydro-4'-hydroxy-spiro[cyclohexane-1,2'-[2*H*]-[1]-benzopyran] (0.2g, 0.67mM) were heated together at 110°C for 6 hrs. Diethylether was added and the precipitated salt was filtered off. The filtrate was concentrated and purified by column chromatography to obtain the desired free amine, which was then dissolved in ethanolic HCl. Solvent was evaporated and the residue obtained was crystallized with ether to obtain the 3',4'-dihydro-3'-hydroxy-4'-(2-(4-methoxy)phenyl)ethylaminospiro [cyclohexane-1,2'-[2*H*]-[1]-benzopyran]. with its HCl salt as a white solid.

Yield 0.076g, 28%. mp 208-209°C (decomp). HPLC purity > 98%.

IR (KBr): 3337, 2923, 1514, 1247 cm^{-1}.

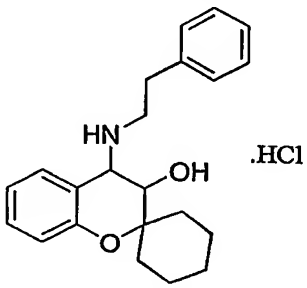
NMR ($CDCl_3$) δ: 1.10 – 2.10 (10H, s), 2.70 – 3.50 (4h, m), 3.74 (3H, s),

4.00 (1H, b), 4.85 (1H, b), 5.38 (1H, br s), 6.70 – 7.20 (7H, m), 7.70 (1H, br s) and 9.80 (2H, m).

MS (M+H) calculated:, observed: 368.31.

EXAMPLE 7

Preparation of 3',4'-dihydro-3'-hydroxy-4'-(2-phenyl)ethylaminospiro [cyclohexane-1,2'-[2*H*]-[1]-benzopyran], hydrochloride



Mixture of 2-phenethylamine (0.199g, 1.646mM) and 3'-bromo-3',4'-dihydro-4'-hydroxy-spiro[cyclohexane-1,2'-[2*H*]-[1]-benzopyran] (0.163g, 0.548mM) were heated together at 100°C for 8 hrs. Diethyl ether was added and the precipitated salt was filtered off. The filtrate was concentrated and purified by column chromatography to obtain the desired free amine, which was then dissolved in ethanolic HCl. Solvent was evaporated and the residue obtained was crystallized with ether to obtain the 3',4'-dihydro-3'-hydroxy-4'-(2-phenyl)ethylaminospiro[cyclohexane-1,2'-[2*H*]-[1]-benzopyran],with its HCl salt as a white solid.

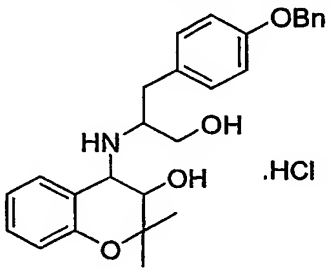
Yield 0.074g, 36%, mp 221°C. HPLC purity > 98%.

IR (KBr): 3281, 2939, 1582, 1491, 1459, 1236, 964, 751 cm^{-1}.

NMR ($CDCl_3$) δ: 1.10 – 2.10 (10H, m), 2.80 (1H, m), 3.20 (2H, m), 3.40 (1H, m), 4.00 (1H, m), 4.83 (1H, d, J = 8.4Hz), 5.40 (1H, br s), 6.93 (1H, d, J = 7.7 Hz), 7.00 (1H, t, 7.3 Hz), 7.13 – 7.28 (5H, m), 7.68 (1H, d, J = 7.3), 9.75 (1H, br s) and 9.94 (1H, br s).

EXAMPLE 8

Preparation of 4-[2-[4-benzyloxyphenyl]-1-hydroxymethyl]ethylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol, hydrochloride



To a solution of 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.445g, 2.53mM) in methanol (1.0ml), 2-(4-benzyloxyphenyl)-1-hydroxymethylethylamine (0.548g, 2.13mM) was added and the reaction mixture was refluxed for 12h. Solvent was removed under reduced pressure and the residue was purified by column chromatography to give the desired free amine (0.577g, 53.0%). Free amine (0.100g, 0.23mM) was then dissolved in ethanolic HCl. Solvent was evaporated under reduced pressure to give the corresponding 4-[2-[4-benzyloxyphenyl]-1-hydroxymethyl]ethylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol hydrochloride salt as a yellowish white solid.

Yield 0.107g, 99.0%. mp.: 70 – 71°C. HPLC purity > 98%.

IR (neat): 3319, 1611, 1583, 1512, 1458, 1246, 1070, 758 cm^{-1}.

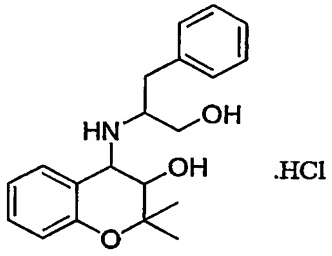
NMR ($CDCl_3$) δ (diastereomeric signals): 1.13 & 1.16 (3H, s), 1.52 & 1.61 (3H, s), 2.95 – 3.20 (2H, m), 3.35 & 3.62 (1H, b), 3.80 & 3.90 (2H, b), 4.20 & 4.50 (1H, m), 4.6 (2H, m), 5.00 & 5.02 (2H, s), 5.27 & 5.36 (1H, d, J=6.2Hz) and 6.76 – 7.40 (13H, m).

HPLC purity > 98%.

MS (M+H) calculated:, observed: 434.2.

EXAMPLE 9

Preparation of 3,4-dihydro-2,2-dimethyl-4-(1-hydroxymethyl-2-phenyl) ethylamino-2*H*-1-benzopyran-3-ol, hydrochloride



To a solution of 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.349g, 1.98mM) in methanol (1.0ml), 1-hydroxymethyl-2-phenylethylamine (0.3g, 1.98mM) was added and the reaction mixture was refluxed for 20h. Solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate. Organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by column chromatography to give the desired free amine, which was then dissolved in ethanolic HCl. Solvent was evaporated under reduced pressure to give the corresponding 3,4-dihydro-2,2-dimethyl-4-(1-hydroxymethyl-2-phenyl)ethylamino-2*H*-1-benzopyran-3-ol hydrochloride salt as a white solid.

Yield 0.128g, 57%.mp.: 73 – 75°C. HPLC purity > 98%.

IR (KBr): 3307, 2977, 1583, 1491, 1458, 1251, 1146, 758 cm^{-1}.

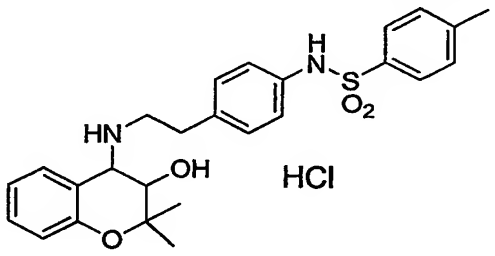
NMR ($CDCl_3$) δ: 1.12 & 1.16 (3H, s), 1.52 (3H, s), 2.90 – 2.10 (4H, m), 3.10 – 3.45 (2H, m), 3.76 & 3.81 (2H, b s), 4.15 & 4.28 (1H, d, J=8.2), 4.65 (1H, m), 6.80 – 7.95 (9H, m), 8.57 & 8.67 (1H, br s), 9.60 & 9.96 (1H, br s).

HPLC purity > 98%.

MS (M+H) calculated: observed: 328.3.

EXAMPLE 10

Preparation of 3,4-dihydro-2,2-dimethyl-4-(2-(4-(4-toluenesulphonylamino)) henyl)ethylamino-2*H*-1-benzopyran-3-ol, hydrochloride



2-(4-(4-toluenesulphonylamino))phenyl)ethylamine, hydrochloride (0.155g, 0.9mM) was dissolved in 4 ml of methanol. To the reaction mixture was added, triethyl amine (0.182g) followed by 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.224g, 1.27 mM). Reaction mixture was stirred at room temperature for 48 hrs. The solvent was removed and the residue was purified on a silica gel column using methanol-chloroform system. Yield of the product was 0.085g. It was then converted into its hydrochloride salt by dissolving in ethanolic HCl. The solvent was evaporated and the residue obtained was recrystallized with isopropyl alcohol to yield the 2,2-Dimethyl-3,4-dihydro-4-(2-(4-(4-toluenesulphonylamino))phenyl)ethylamino-2*H*-1-benzopyran-3-ol as a white crystalline solid.

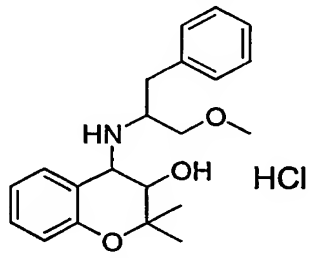
Yield 0.049 g, 16%, mp > 200°C

IR (KBr): 3392, 2979, 1613, 1584, 1514, 1492, 1460, 1372, 1338, 1306, 1253, 1159, 1092, 929, 815, 760 cm^{-1}.

NMR ($CDCl_3$, few drops DMSO) δ: 1.15 (3H, s), 1.51 (3H, s), 2.36 (3H, s), 3.04-3.18 (4H, m), 3.97 (1H, br s), 4.44 (1H, br s), 5.97 (1H, s), 6.82-7.7 (12H, m), 9.43 (1H, s), 9.81-10.06 (2H, m).

EXAMPLE 11

Preparation of 3,4-dihydro-2,2-dimethyl-4-[1-methoxymethyl-2-phenyl] ethylamino-2*H*-1-benzopyran-3-ol, hydrochloride



To a solution of 1-methoxymethyl-2-phenylethylamine, hydrochloride (0.197g, 0.98mM) in methanol (0.5ml), triethylamine (0.148g, 1.47mM) was added and the reaction mixture was stirred at room temperature for 20 min. 3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.258g, 1.47mM) was then added and the reaction mixture was further stirred for 48h at room temperature. Solvent was removed under reduced pressure and ethyl acetate was added to the residue. Organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Solvent was evaporated under reduced pressure and the residue was purified by column chromatography to give the desired free amine. It was then dissolved in ethanolic HCl. Solvent was evaporated

under reduced pressure to give the corresponding hydrochloride salt as a white solid, which was then purified by crystallization from ethyl acetate as a crystalline solid.

Yield 0.111g, 30.0%. mp: >200°C.

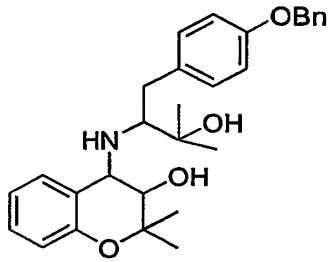
IR (KBr): 3288, 2925, 1598, 1457, 1247, 1099, 763 cm^{-1}.

NMR (DMSO-d_6) δ: 1.08 (3H, s), 1.44 (3H, s), 3.14 (3H, s), 2.90 – 3.50 (4H, m), 4.05 (2H, b), 4.56 (1H, br), 6.39 (1H, br), 6.85 (1H, d, J=7.7Hz), 7.02 (1H, t, J=7.0Hz), 7.20 – 7.40 (6H, m), 7.74 (1H, br s), 9.04 (1H, br s) and 9.19 (1H, br s)

MS (M+H) calculated:, observed: 342.1.

EXAMPLE 12

Preparation of 4-((4-(4-benzyloxy)phenyl)-2-hydroxy-2-methyl)but-3-ylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol



To a solution of 4-(4-benzyloxy)phenyl-2-hydroxy-2-methylbut-3-ylamine, hydrochloride (0.170g, 0.59mM) and 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.170g, 0.59mM) in methanol (0.5ml), triethylamine (0.090g, 0.894mM) was added and the reaction mixture was refluxed for 24h. Solvent was evaporated under reduced pressure and ethyl acetate was added to the residue. Organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Solvent was then evaporated under reduced pressure and the residue was purified by column chromatography to give the 4-((4-(4-benzyloxy)phenyl)-2-hydroxy-2-methyl)but-3-ylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol.

Yield 0.028g, 10%. mp.: 94°C, HPLC purity > 98%.

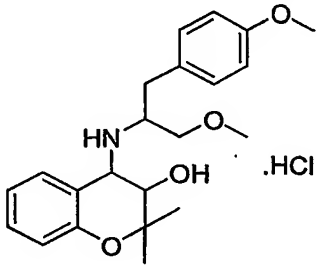
IR (KBr): 3306, 2973, 2929, 1609, 1583, 1512, 1249, 1075, 757 cm^{-1}.

NMR ($CDCl_3$) (diastereomeric signals) δ: 0.90 – 1.70 (12H, m), 3.00 (1H, m), 3.25 – 3.60 (2H, m), 4.00 – 4.40 (3H, m), 4.99 & 5.01 (2H, s), 5.60 (1H, m), 6.65 – 7.40 (13H, m).

MS (M+H) calculated: observed: 462.2.

EXAMPLE 13

Preparation of 3,4-dihydro-2,2-dimethyl-4-(1-methoxymethyl-2-(4-methoxy)phenyl)ethylamino-2*H*-1-benzopyran-3-ol, hydrochloride



To a solution of 1-methoxymethyl-2-(4-methoxy)phenylethylamine, hydrochloride (0.131g, 0.568mM) in methanol (0.2ml), triethylamine (0.086g, 0.852mM) was added and the reaction mixture was stirred at room temperature for 20 min. 3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.1g, 0.568mM) was then added and the reaction mixture was further stirred for 48h at room temperature. Solvent was removed under reduced pressure and ethyl acetate was added to the residue. Organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Solvent was then evaporated under reduced pressure and the residue was purified by column chromatography to give the desired free amine, which was then dissolved in ethanolic HCl. Solvent was evaporated under reduced pressure to give the corresponding 3,4-dihydro-2,2-dimethyl-4-(1-methoxymethyl-2-(4-methoxy)phenyl)ethylamino-2*H*-1-benzopyran-3-ol hydrochloride salt as a white solid.

Yield 0.119g, 57%. mp. 142°C. HPLC purity > 98%.

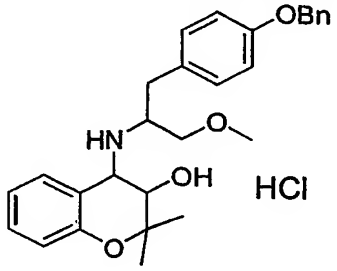
IR (KBr): 3271, 2977 2935, 1514, 1249, 1035 cm^{-1}.

NMR ($CDCl_3$) δ: NMR ($CDCl_3$) δ: 1.18 (3H, s), 1.53 (3H, s), 3.30 (3H, s), 3.12 – 3.39 (2H, m), 3.4-3.7 (3H, m), 4.20 (1H, m), 4.24 (1H, d, J=8.4 Hz), 5.60 (1H, d, J = 5.13 Hz), 6.80 – 6.95 (4H, m), 7.01 (2H, d, J = 8.4 Hz), 7.25-7.39 (4H, m), 8.51 (1H, br s).

MS (M+H) calculated:, observed: 327.2.

EXAMPLE 14

Preparation of 4-[2-[4-benzyloxyphenyl]-1-methoxymethyl]ethylamino-3, 4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol, hydrochloride



To a solution of 2-(4-benzyloxy)phenyl-1-methoxymethylethylamine, hydrochloride (0.175g, 0.568mM) in methanol (0.4ml), triethylamine (0.086g, 0.852mM) was added and the reaction mixture was stirred at room temperature for 20 min. 3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.1g, 0.568mM) was then added and the reaction mixture was further stirred for 48h at room temperature. Solvent was removed under reduced pressure and ethyl acetate was added to the residue. Organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Solvent was then evaporated under reduced pressure and the residue was purified by column chromatography to give the desired free amine, which was then dissolved in ethanolic HCl. Solvent was evaporated under reduced pressure to give the corresponding 4-[2-[4-benzyloxyphenyl]-1-methoxymethyl]ethylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol hydrochloride salt as a white solid.

Yield 0.586g, 73%. mp.: 155°C. HPLC purity > 98%.

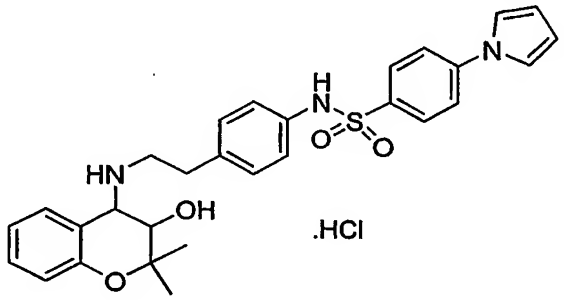
IR (KBr): 3352, 2971,2927, 2787, 1584, 1513, 1488, 1454, 1258, 1089, 768, 744 cm^{-1}.

NMR ($CDCl_3$) δ: 1.18 & 1.19 (3H, s), 1.53 & 1.55 (3H, s), 3.30 & 3.40 (3H, s), 3.09 – 3.65 (5H, m), 4.22 & 4.32 (1H, m), 4.60 & 4.90 (1H, d, J=8.0), 5.02 (2H, s), 5.45 & 5.57 (1H, d, J=4.8Hz), 6.80 – 7.10 (6H, m), 7.20 – 7.70 (7H, m), 7.96 & 8.65 (1H, br s) 10.17 & 11.09 (1H, br s).

MS (M+H) calculated:, observed: 448.2.

EXAMPLE 15

Preparation of 3,4-dihydro-2,2-Dimethyl-4-(2-(4-(1-pyrrolo) benzenesulphonylamino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol hydrochloride



2-(4-(1-pyrrolo)benzenesulphonylamino)phenyl)ethylamine.hydrochloride (0.148g, 0.392 mM) was dissolved in 1.5 ml of methanol. To the reaction mixture was added, triethyl amine (0.059g) followed by 3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.096g, 0.54 mM). Reaction mixture was stirred at room temperature for 48 hrs. The solvent was removed and the residue was purified on a silica gel using $CHCl_3 \rightarrow 2\%MeOH/CHCl_3$ solvent system. The desired amine (0.067g) was converted into its hydrochloride salt using ethanolic HCl and dichloromethane as solvent. Solvents were evaporated and the residue was recrystallized using ethyl acetate – hexane to obtain the desired compound as a white solid.

Yield of 0.065g, 30% . mp >200°C. HPLC purity >97%.

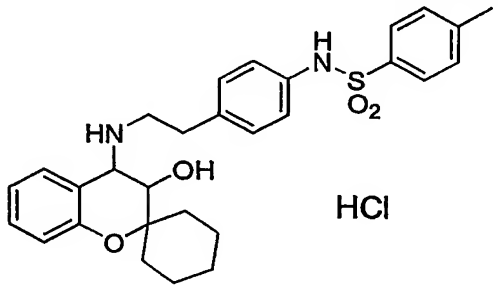
IR (KBr): 3240, 1597,1510, 1335, 1164, 1093, 1064, 747 cm^{-1}.

NMR (DMSO) δ: 1.07 (3H, s), 1.40 (3H, s), 2.65-3.2 (4 H, m), 3.93 (1 H, d, J = 9.16 Hz), 4.32-4.36 (1H, br s), 6.31 (2H, t, J = 2.02 Hz), 6.83 (1H, d, J = 8.05 Hz),), 6.97 (1H, t, J = 7.5 Hz), 7.02 (2H, d, J = 9.15 Hz), 7.09 (2H, d, J = 8.79 Hz), 7.26 (1H, t, J = 7.87 Hz), 7.46 (1H, t, J = 2.2 Hz), 7.62 (1H, d, J = 8.42 Hz), 7.73-7.80 (4H, m), 9.08 (1H, br s), 9.50 (1H, br s), 10.29 (1H, s).

MS (M+H): Observed and calculated 518.4.

EXAMPLE 16

Preparation of 3',4'-dihydro-3'-hydroxy-4'-(2-(4-(4-toluenesulphonylamino)) phenyl)ethylamino spiro[cyclohexane-1,2'-[2*H*]-[1]-benzopyran], hydrochloride



2-(4-(4-toluenesulphonylamino))phenyl)ethylamine, hydrochloride (0.2g, 0.614 mM) was dissolved in 2 ml of methanol. To the reaction mixture was added, triethyl amine (0.093g) followed by 3',4'-dihydro-3',4'-epoxyspiro[cyclohexane-1,2'-[2*H*]-[1]-benzopyran] (0.185g, 0.856 mM). Reaction mixture was stirred at room temperature for 48 hrs. The solvent was removed and the residue was purified on a silica gel column using methanol-chloroform system. Yield of the product was 0.13g. It was then converted into its hydrochloride salt by dissolving in ethanolic HCl. The solvent was evaporated to obtain 3',4'-dihydro-3'-hydroxy-4'-(2-(4-(4-toluenesulphonylamino)) phenyl)ethylamino spiro[cyclohexane-1,2'-[2H]-[1]-benzopyran], compound as a white solid.

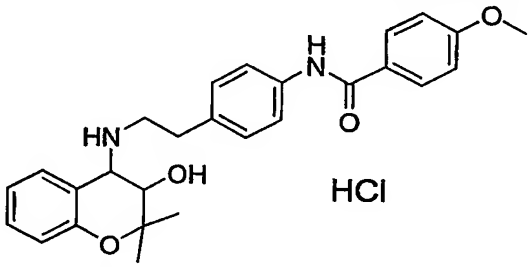
mp: 158°C. Yield 0.139 g, 42%. HPLC purity > 98%.

IR (KBr): 3351, 2931, 2859, 1613, 1584, 1514, 1492, 1460, 1337, 1306, 1239, 1158, 1093, 961, 928 cm^{-1}.

NMR ($CDCl_3$, few drops DMSO) δ: 1.10 – 2.00 (10H, m), 2.35 (3H, s), 2.85 – 3.20 (4H, m), 3.60 (1H, m), 3.82 (1H, d, J=9.3Hz), 4.45 (1H, d, J=9.3Hz), 6.90 – 7.65 (12H, m). MS (M+H) calculated:, observed: 507.2.

EXAMPLE 17

Preparation of 3,4-Dihydro-2,2-dimethyl-4-(2-(4-(4-methoxy)benzamido)phenyl)ethylamino-2*H*-1-benzopyran-3-ol . Hydrochloride



2-(4-(4-methoxy)benzamido)phenyl)ethylamine, hydrochloride (0.15g, 0.489mM) was dissolved in 2 ml of methanol. To the reaction mixture was added, triethyl amine (0.074g) followed by 3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.12g, 0.682mM). Reaction mixture was refluxed for 3 hrs and at room temperature for additional 14 hrs. The solvent was removed and the residue was purified on a silica gel column using methanol-chloroform system. The 3,4-dihydro-2,2-Dimethyl-4-(2-(4-(4-methoxy)benzamido)phenyl)ethylamino-2*H*-1-benzopyran-3-ol was obtained as a white solid.

Yield 0.074g, 34%.mp: 110°C. HPLC purity > 98%.

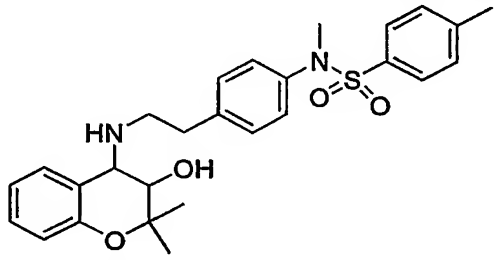
IR (KBr): 3326, 2931, 1646, 1606, 1515, 1484, 1306, 1254, 1175, 1030, 932, 841, 758 cm^{-1}.

NMR (CD_3OD) δ: 1.12 (3H, s), 1.42 (3H, s), 2.65 – 2.90 (4H, m), 3.67 (1H, d, J=9.3Hz), 3.78 (1H, d, J=9.3Hz), 3.86 (3H, s), 6.71 (1H, d, J=7.8Hz), 6.87 (1H, t, J=7.2Hz), 7.02 (2H, d, J=8.7Hz), 7.10 (1H, t, J=7.8Hz), 7.20 (2H, d, J=8.4Hz), 7.29 (1H, d, J=7.8Hz), 7.59 (2H, d, J=8.4Hz), 7.90 (2H, d, J=8.7Hz).

MS (M+H) calculated:, observed: 447.2.

EXAMPLE 18

Preparation of 3,4-Dihydro-2,2-dimethyl-4-(2-(*N'*-methyl-4-(toluenesulphonyl)amino)phenyl)ethyl amino-2*H*-1-benzopyran-3-ol, hydrochloride



2-(*N*-methyl-4-toluenesulphonylamino)phenyl)ethyl amine, hydrochloride (0.16g, 0.469mM) was dissolved in 2 ml of methanol. To the reaction mixture was added, triethyl amine (0.071g) followed by 3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.131g, 0.744mM). Reaction mixture was stirred at room temperature for 24 hrs. The solvent was removed and the residue was purified on a silica gel column using methanol-chloroform system. Yield of the product was 0.107g. It was then converted into its hydrochloride salt by dissolving in dichloromethane followed by addition of ethanolic HCl. The solvent was evaporated and the residue obtained was recrystallized with isopropyl alcohol to yield 3,4-dihydro-2,2-Dimethyl-4-(2-(*N*-methyl-4-toluenesulphonylamino)phenyl)ethyl amino-2*H*-1-benzopyran-3-ol compound) as a white crystalline solid.

Yield 0.072g, 30%.mp: >200°C. HPLC purity > 98%.

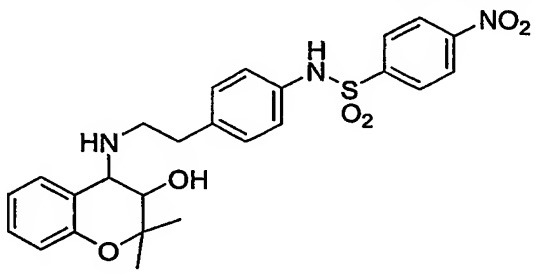
IR (KBr): 3495, 2981, 1509, 1491, 1461, 1340, 1172, 1152, 1059, 773, 581 cm^{-1}.

NMR (CD_3OD) δ: 1.09 (3H, s), 1.42 (3H, s), 2.38 (3H, s), 3.07 (3H, s), 2.90 – 3.30 (4H, m), 4.05 (1H, m), 4.41 (1H, d, J=8.8Hz), 6.33 (1H, d, J=5.8Hz), 6.85 (1H, d, J=7.3Hz), 6.97 – 7.05 (3H, m), 7.18 – 7.40 (6H, m), 7.80 (1H, d, J=7.7Hz), 9.40 (1H, br s), 9.90 (1H, br s). HPLC purity > 98%.

MS (M+H) calculated:, observed: 447.2.

EXAMPLE 19

Preparation of 3,4-Dihydro-2,2-dimethyl-4-(2-(4-(4-nitro)benzenesulphonyl) amino) phenyl)ethylamino-2*H*-1-benzopyran-3-ol



2-(4-nitrobenzenesulphonylamino)phenyl)ethylamine, hydrochloride (0.17g, 0.47mM) was dissolved in 0.5 ml of methanol. To the reaction mixture was added, triethyl amine (0.071g) followed by 3,4-Dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.083g, 0.47mM). Reaction mixture was refluxed for 14 hrs. The solvent was removed and the residue was taken up in ethyl acetate. The organic layer was washed with water, brine, and anhydrous Na_2SO_4. It was then concentrated and the resulting compound was purified on a silica gel column using methanol-chloroform system to obtain the 3,4-dihydro-2,2-Dimethyl-4-(2-(4-nitrobenzenesulphonylamino) phenyl)ethylamino-2*H*-1-benzopyran-3-ol as a yellow fluffy solid.

Yield 0.101g, 43%, mp 67°C. HPLC purity > 98%.

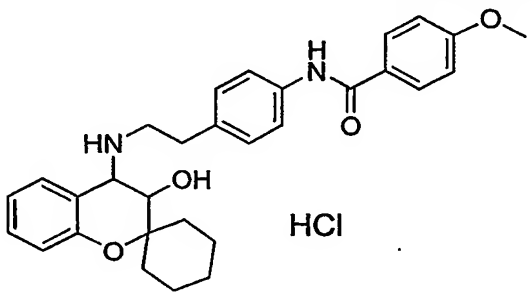
IR (KBr): 3271, 2928, 1531, 1349, 1165, 737 cm^{-1}.

NMR ($CDCl_3$) δ: 1.17 (3H, s), 1.47 (3H, s), 2.75 – 2.96 (10H, m), 3.48 (1H, d, J=9.9Hz), 3.64 (1H, d, J=9.9Hz), 6.77 – 6.87 (2H, m), 7.00 – 7.14 (6H, m), 7.90 (2H, d J=8.7Hz), 8.27 (2H, d J=8.7Hz).

MS (M+H) calculated:, observed: 498.1.

EXAMPLE 20

Preparation of 3',4'-dihydro-3'-hydroxy-4'-(2-(4-(4-methoxy)benzamido))phenyl) ethylaminospiro [cyclohexane-1,2'-[2*H*]-[1]-benzopyran], hydrochloride



To a suspension of 2-(4-methoxybenzamido)phenyl)ethylamine, hydrochloride (0.2g, 0.65mM) in 1 ml of methanol, was added, triethylamine (0.098g) followed by 3',4'-dihydro-3',4'-epoxyspiro[cyclohexane-1,2'-[2*H*]-[1]-benzopyran] (0.14g, 0.65mM). Reaction mixture was stirred at room temperature for 40 hrs. The solvent was removed and after the usual workup the residue was purified on a silica gel column using methanol-chloroform system. The desired product was obtained as a white solid with a yield of 0.141g (44%). Some of this compound (100 mg) was converted to its hydrochloride salt and this salt was recrystallized with isopropanol to obtain the desired compound 3',4'-dihydro-3'-hydroxy-4'-(2-(4-methoxybenzamido)phenyl) ethylaminospiro [cyclohexane-1,2'-[2*H*]-[1]-benzopyran] as a white solid.

Yield 0.04g, 12%. mp -180°C. HPLC purity > 98%.

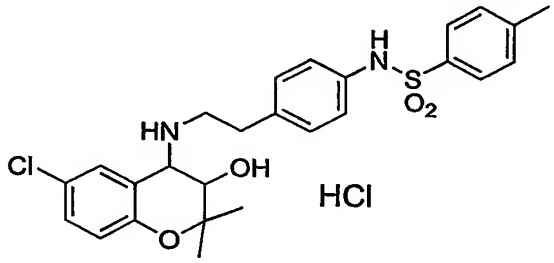
IR (KBr): 3326, 2931, 1606, 1515, 1255, 1031, 763 cm^{-1}.

NMR ($CDCl_3$) δ: 1.20 – 2.00 (10H, m), 2.90 – 3.20 (4H, m), 3. 80 (4H, b), 4.49 (1H, d, J=9.3Hz), 6.93 – 7.06 (4H, m), 7.20 – 7.38 (4H, m), 7.65 (2H, d J=7.8Hz), 7.91 (2H, d J=8.7Hz).

MS (M+H) calculated:, observed: 487.2.

EXAMPLE 21

Preparation of 6-Chloro-2,2-dimethyl-3,4-dihydro-4-(2-(4-(4-toluenesulphonylamino))phenyl)ethyl amino-2*H*-1-benzopyran-3-ol, hydrochloride



2-(4-(4-toluenesulphonylamino))phenyl)ethyl amine, hydrochloride (0.109g, 0.63mM) was dissolved in of methanol (1.5ml). To the reaction mixture was added, triethyl amine (0.095g) followed by 6-chloro-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.162g, 0.76mM). Reaction mixture was stirred at room temperature for 48 hrs. The solvent was removed and the residue was purified on a silica gel column using methanol-chloroform system. Yield of the product was 0.085g. It was then converted into its hydrochloride salt by dissolving in ethanolic HCl. The solvent was evaporated to obtain the 6-chloro-2,2-Dimethyl-3,4-dihydro-4-(2-(4-(4-toluenesulphonylamino))phenyl)ethyl amino-2*H*-1-benzopyran-3-ol as a white solid. mp 193°C (decomp.).

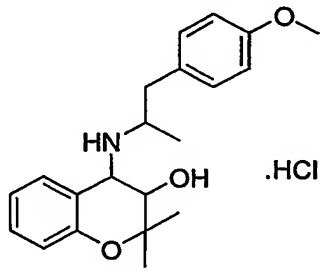
Yield 0.07g, 29%. mp 193°C (decomp.). HPLC purity > 97%.

IR (KBr): 3233, 2978, 2714, 1586, 1482, 1340, 1159, 1092 cm^{-1}.

NMR ($CDCl_3$) δ: 1.37 (3H, s), 1.50 (3H, s), 2.36 (3H, s), 3.00 – 3.30 (3H, m), 3.99 (1H, d, J=8.8Hz), 4.40 (1H, d, J=8.0Hz),), 6.79 (1H, d, J=8.8Hz), 7.00 – 7.20 (3H, m), 7.20 – 7..30 (3H, m), 7.42 (1H, s), 7.60 – 7.80 (3H, m), 9.48 (1H, br s), 9.93 (2H, br s).

EXAMPLE 22

Preparation of 3,4-Dihydro-2,2-dimethyl-4-[[3-[4-methoxy]phenyl] prop-2-yl]amino-*2H*-1-benzopyran-3-ol. Hydrochloride



To a solution of 2-amino-3-[4-methoxy]phenyl propane.hydrochloride (0.115g, 0.568 mM) in 0.2 ml of methanol was added triethylamine (0.5 ml). The reaction mixture was stirred for 20 minutes and to it was added a solution of 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2H-1-benzopyran (0.1g, 0.568 mM) in 0.2 ml of methanol. The reaction mixture was stirred for 48 hrs. It was then concentrated and the residue obtained was purified on a silica gel column using methanol/chloroform solvent system. The desired amine was obtained as an oil. It was converted to its corresponding hydrochloride salt by dissolving it in chloroform and ethanolic HCl. The solvents were removed to obtain the desired compound as a white solid.

Yield 0.073g, 34%. mp 99°C.

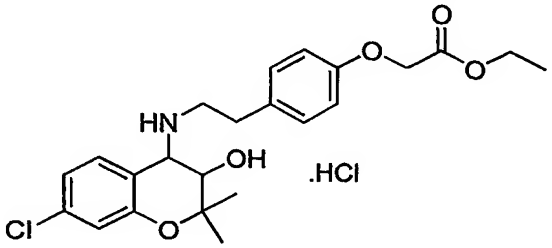
IR (KBr): 3369, 2929, 1612, 1584, 1514, 1492, 1460, 1303, 1250, 1147, 1072, 937, 758 cm^{-1}.

NMR (Diastereomers, $CDCl_3$) δ: 1.15 & 1.17 (3H, s), 1.36 & 1.49 (3H, d, J = 6.2 Hz), 1.52 (3H, s), 2.8-3.0 (1H, m), 3.25-3.6 (2H, m), 3.76, 3.77 (3H, s), 4.23 (1H, br s), 4.45, 4.64 (1H, d, J = 8 Hz)), 5.37, 5.42 (1H, br s), 6.7-7.7 (8H, m), 8.18, 9.45, 9.87, 10.47 (2H, br s).

MS (M+H): calculated & observed 342.3.

EXAMPLE 23

Preparation of 2-[4-[*N*-[7-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy] acetic acid ethyl ester.Hydrochloride



To a solution of 4-[*N*-t-Boc-*N*-[7-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2H-1benzopyran-4-yl]aminoethyl]phenoxy acetic acid ethyl ester (0.3g, 0.56 mM) in 20 ml of ethanol was bubbled dry HCl gas for 10 min. The reaction mixture was capped and stirred for 18 hrs at room temperature. The solvent was evaporated to dryness to obtain the desired compound as a white solid.

Yield of 0.253g, 95%. mp 199-202°C.

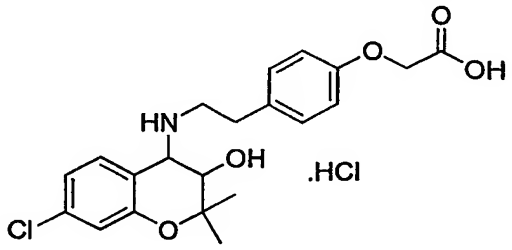
IR (KBr): 3172, 2903, 2608, 1763, 1608, 1515, 1489, 1438, 1303, 1211, 1179, 1084, 957, 948, 830 cm^{-1}.

NMR (CD_3OD) δ: 1.18 (3H, s), 1.28 (3H, t, J = 7.3 Hz), 1.49 (3H, s), 2.84-3.0 (1H, m), 3.0-3.2 (2H, m), 3.3-3.42 (1H, m), 3.93 (1H, d, J = 9.9 Hz), 4.24 (2H, q, J = 7.3 Hz), 4.43 (1H, d, J = 9.1 Hz), 4.70 (2H, s), 6.90-6-95 (3H, m), 7.34 (1H, dd, J = 2.2 & 8.4 Hz), 7.15-7.26 (3H, m).

MS (M+H): calculated & observed 433.18.

EXAMPLE 24

Preparation of 2-[4-[*N*-[7-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy] acetic acid.Hydrochloride



To a solution of 4-[*N*-[7-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy acetic acid ethyl ester (0.1g, 0.21 mM) in 10 ml of ethanol was added 5 equivalents of aqueous NaOH. The reaction mixture was stirred for 20 hrs. The organic solvent was evaporated and the reaction mixture was cooled to

0°C. It was acidified with 1N HCl. The aqueous layer was extracted in EtOAc. The organic layer was dried and concentrated to obtain the desired compound as a semi-solid.

Yield of 0.087g (93%).

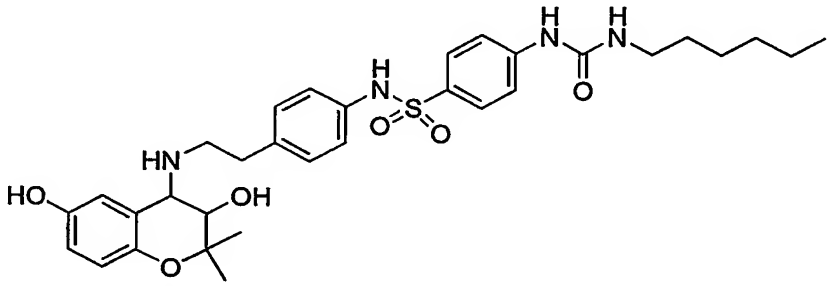
IR (KBr): 3307, 2930, 1732, 1606, 1575, 1515, 1489, 1303, 1233, 1079, 955 cm^{-1}.

NMR (CD_3OD) δ: 1.8 (3H, s), 1.49 (3H, s), 2.85-3.4 (4H, m), 3.93 (1H, d, J = 9.9 Hz), 4.43 (1H, d, J = 9.5 Hz), 4.64 (2H, s), 6.88-6-96 (3H, m), 7.04 (1H, dd, J = 2.2 & 8.4 Hz), 7.16-7.27 (3H, m).

MS (M+H): calculated & observed 406.2.

EXAMPLE 25

Preparation of 3,4-Dihydro-2,2-dimethyl-4-[2-[4-[4-[3-[Hex-1-yl]]urido]benzenesulfonamido]phenyl]ethylamino- 2*H*-1-benzopyran-3,6-diol



To a stirred suspension of [2-[4-[4-[3-[hex-1-yl]]urido] benzenesulfonamido]phenyl]ethylamine.HCl (0.52g, 1.14 mM) in 0.5 mL of methanol was added triethyl amine (0.115g, 1.14 mM). The mixture was stirred for 20 min and 6-benzyloxy-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.2g, 0.71 mM) was added. The reaction mixture was stirred at room temperature for 48 hrs. After a standard workup it was purified by column chromatography to afford 0.34g (68%) of 6-benzyloxy-3,4-dihydro-2,2-dimethyl-4-[2-[4-[4-[3-[hex-1-yl]]urido]benzenesulfonamido]phenyl] ethylamino-2*H*-1-benzopyran-3-ol. 0.2g of this product was dissolved in 1ml of methanol and 80 mg of Pd/C catalyst was added. The reaction was stirred overnight under hydrogen atmosphere. The reaction mixture was filtered through celite and concentrated to obtain the desired compound as a white solid.

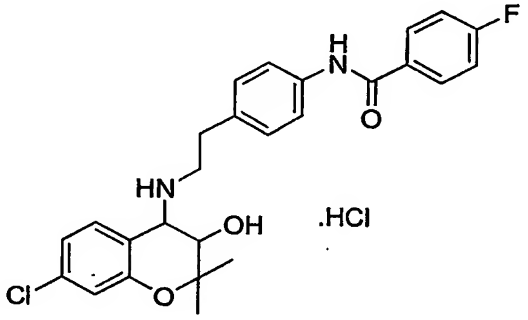
Yield 0.14g (80%) , m.p. 162°C.

IR[KBr]: 3391, 2930, 1673, 1591, 1544, 1497, 1461, 1329, 1231, 1153, 1093 cm^{-1}.

NMR[CD_3OD] δ: 0.9 (3H, m), 1.1 (3H, s), 1.26-1.54 (11H, m), 2.8-3.1 (4H, m), 3.15 (2H, t, J = 6.9 Hz), 3.78 (1H, d, J = 9.3 Hz), 4.14 (1H, d, J = 9.3 Hz), 6.64 (1H, d, J = 9 Hz), 6.69 (1H, d, J = 9 Hz), 6.79 (1H, s), 7.03 (2H, d, J = 8.7 Hz), 7.09 (2H, d, J = 8.4 Hz), 7.4 (2H, d, J = 9 Hz), 7.58 (2H, d, J = 9 Hz).

EXAMPLE 26

Preparation of 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-(4-fluoro) benzamido)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride



2-(4-(4-Fluoro)benzamido)phenyl)ethylamine, hydrochloride (0.15g, 0.5 mM) was dissolved in 0.5 ml of methanol. To the reaction mixture was added, triethyl amine (0.081g) followed by 3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.106g, 0.5 mM). Reaction mixture was stirred at room temperature for 36 hrs. The solvent was removed and the residue was purified on a silica gel column using methanol-chloroform system. The desired amine was obtained as a white solid. It was then converted into its hydrochloride salt using standard method.

Yield 0.2g (85%). mp: >200°C.

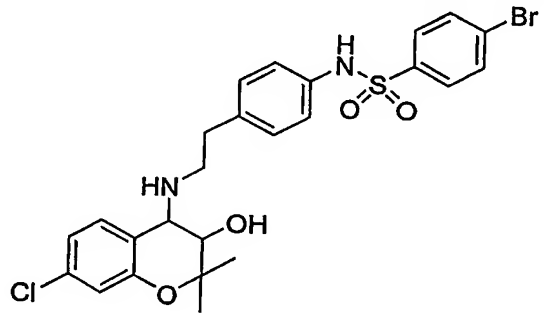
IR (KBr): 3414, 2926, 2859, 1644, 1604, 1515, 1412, 1318 cm^{-1}.

NMR (CD_3OD) δ: 1.19 (3H, s), 1.50 (3H, s), 2.95 – 3.55 (4H, m), 3.94 (1H, d, J=9.5Hz), 4.95 (1H, d, J=9.5 Hz), 6.94 (1H, d, J=2.2 Hz), 7.05 (1H, dd, J = 2.2 & 8.4 Hz), 7.25-7.30 (5H, m), 7.68 (2H, d, J = 8.4 Hz), 8.0 (2H, m).

MS (M+H) calculated:, observed: 469.2.

EXAMPLE 27

Preparation of 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-(4-bromo benzene sulphonyl amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol



2-(4-(4-Bromo)benzene sulphonyl amino)phenyl)ethylamine, hydrochloride (0.12g, 0.3 mM) was dissolved in 0.5 ml of methanol. To the reaction mixture was added, triethyl amine (0.045g) followed by 7-chloro-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.064g, 0.3 mM). Reaction mixture was stirred at room temperature for 100 hrs. The solvent was removed and the residue was purified on a silica gel column using methanol-chloroform system to obtain the desired compound as a white solid.

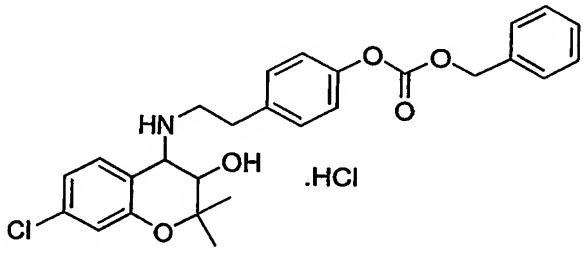
Yield 0.06 g (35%), m.p. 79-80°C.

IR (KBr): 2929, 1574, 1511, 1475, 1160, 1089, 821 cm^{-1}.

NMR ($CDCl_3$) δ: 1.15 (3H, s), 1.46 (3H, s), 2.65 – 2.95 (4H, m), 3.49 (1H, d, *J*=9.9 Hz), 3.64 (1H, d, *J*=9.9 Hz), 6.8 (2H, m), 6.92 (1H, d, *J*=8.7 Hz), 6.98 (2H, d, *J*= 8.4 Hz), 7.08 (2H, d, *J* = 8.4), 7.54 (2H, d, *J* = 9 Hz), 7.58 (2H, d, *J* = 8.7 Hz).

EXAMPLE 28

Preparation of Carbonic acid, phenylmethyl-4-(*N*-(7-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl) aminoethyl)phenyl ester.Hydrochloride.



To a solution of *N*-t-Boc-*N*-[7-Chloro-3,4-dihydro-2,2-dimethyl- 4-(2-(4-hydroxyphenyl)]ethylamino-2*H*-1-benzopyran-3-ol (0.1g, 0.223 mM) in 5 ml of acetone was added potassium carbonate (0.046g) and benzylchloroformate (0.038g, 0.223 mM).

The reaction mixture was stirred for 20 hrs. The reaction mixture was filtered and the filtrate was concentrated. The residue was washed with EtOAc to obtain the crude product. This crude product (0.11g, 0.18 mM) was dissolved in 20 ml of dichloromethane and HCl gas was bubbled through it. The reaction mixture was capped and stirred for 20 hrs. The solvent was evaporated to obtain the desired product as a white solid.

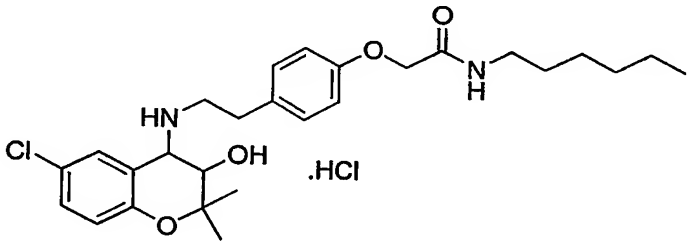
Yield of 0.08g (83%), m.p. 175-176°C.

IR (KBr): 3307, 2977, 2725, 1761, 1573, 1490, 1218, 1079, 954, 696 cm^{-1}.

NMR (CD_3OD) δ: 1.18 (3H, s), 1.49 (3H, s), 2.95-3.45 (4H, m), 3.95 (1H, d, J = 9 Hz), 4.43 (1H, d, J = 9 Hz), 5.24 (2H, s), 6.90 (1H, d, J = 2.1 Hz), 7.04 (1H, dd, J = 2.2 & 8.4 Hz), 7.14-7.17 (3H, m), 7.23-7.31 (4H, m), 7.35-7.40 (3H, m).

EXAMPLE 29

Preparation of 2-[4-[*N*-[6-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy] acetamide-*N*'-hex-1-yl.Hydrochloride



To a solution of 2-[4-[*N*-Boc-*N*-[6-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy] acetic acid ethyl ester (0.1g, 0.187 mM) in 3 ml of THF was added n-hexyl amine (0.095g, 0.935 mM) and 0.5 ml water. The reaction mixture was stirred for 5 hrs. The solvent was evaporated and the residue was taken up in EtOAc. The organic layer was dried and evaporated to obtain the crude product of which 0.1g (0.17 mM) was dissolved in dichloromethane and HCl gas was bubbled through it. The reaction mixture was stirred for 20 hrs and then evaporated to dryness. The residue was washed with ether to obtain the desired compound as a white solid.

Yield 0.07g (86%), m.p. 159-161°C.

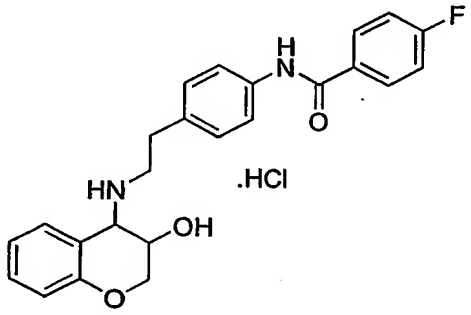
IR (KBr): 3245, 2929, 1656, 1511, 1243, 1095, 1078, 823 cm^{-1}.

NMR (DMSO) δ: 0.84 (3H, t, J = 6.6 Hz), 1.08 (3H, s), 1.22-1.45 (8H, m), 1.42 (3H, s), 2.9-3.2 (6H, m), 4.0 (1H, br s), 4.35-4.5 (3H, m), 6.29 (1H, br s), 6.85-

6.9 (3H, m), 7.14 (2H, d, J = 8.4 Hz), 7.3 (1H, dd, J = 2.1 & 8.7 Hz), 7.90 (1H, s), 7.99 (1H, t, J = 5.4 Hz), 9.26 (1H, br s), 9.75 (1H, br s).

EXAMPLE 30

Preparation of 3,4-Dihydro-4-(2-(4-(4-fluoro)benzamido)phenyl) ethylamino)-2*H*-1-benzopyran-3-ol.Hydrochloride



2-(4-(4-Fluoro)benzamido)phenyl)ethylamine, hydrochloride (0.13g, 0.44 mM) was dissolved in 2 ml of methanol. To the reaction mixture was added, triethyl amine (0.066g) followed by 3,4-dihydro-3,4-epoxy-2*H*-1-benzopyran (0.09g, 0.62 mM). Reaction mixture was stirred at room temperature for 48 hrs. The solvent was removed and the residue was purified on a silica gel column using methanol-chloroform system. The desired amine was obtained as a white solid with a yield of 0.04g (24%). This compound was dissolved in chloroform and HCl gas was bubbled through it . Solvent was evaporated to obtain the desired compound.

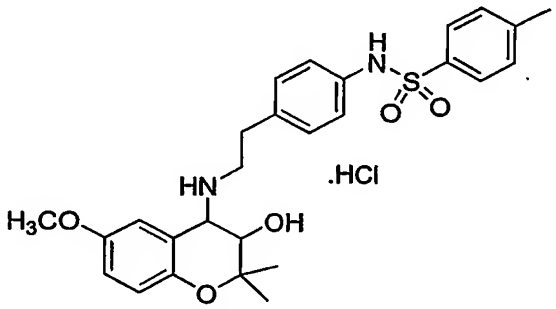
Yield : 0.03g (15%). mp: 194°C.

IR (KBr): 3369, 2929, 2744, 1655, 1603, 1533, 1495, 1416, 1324, 1230, 851, 759 cm^{-1}.

NMR (DMSO-d_6OD) δ: 2.99 (2H, t, J = 8.1 Hz), 4.10-4.14 (1H, m), 4.26-4.38 (3H, m), 5.79 (1H, br s), 6.88 (1H, d, J = 8.4 Hz), 6.97 (1H, t, J = 7.2 Hz), 7.23-7.37 (5H, m), 7.50 (1H, d, J = 7.5 Hz), 7.7 (2H, d, J = 8.4 Hz), 7.99-8.04 (2H, m), 9.03 (1H, br s), 9.33 (1H, br s), 10.23 (1H, s).

EXAMPLE 31

Preparation of 3,4-Dihydro-2,2-dimethyl-6-methoxy-4-(2-(4-(4-toluenesulphonyl amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride



2-(4-(4-Toluene sulphonyl amino)phenyl)ethylamine, hydrochloride (0.11g, 0.336 mM) was dissolved in 1.5 ml of methanol. To the reaction mixture was added, triethyl amine (0.05g) followed by 3,4-dihydro-2,2-dimethyl-3,4-epoxy-6-methoxy-2*H*-1-benzopyran (0.083g, 0.404 mM). Reaction mixture was stirred at room temperature for 48 hrs. The solvent was removed and the residue was purified on a silica gel column using methanol-chloroform system to obtain the amine (0.069g, 42%). It was then converted to its hydrochloride salt using conventional method to obtain the desired compound as a white solid.

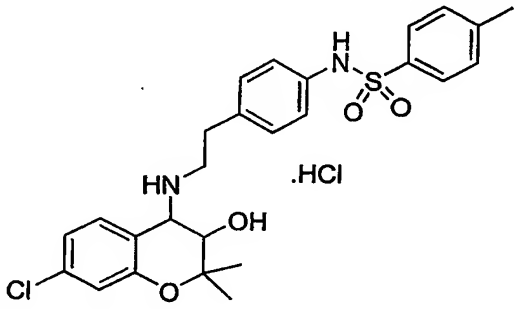
Yield of 0.04g (22%), m.p. 141°C.

IR (KBr): 3250, 2978, 2927, 1499, 1235, 1157, 1092 cm^{-1}.

NMR (DMSO-d_6) δ: 1.04 (3H, s), 1.38 (3H, s), 2.32 (3H, s), 2.84 – 3.04 (4H, m), 3.70 (3H, s), 3.92 (1H, d, J=8.7 Hz), 4.3 (1H, br s), 6.74 (1H, d, J= 9 Hz), 6.84 (1H, dd, J= 2.1 & 8.7 Hz), 7.0 (2H, d, J= 8.7), 7.06 (2H, d, J= 8.1 Hz), 7.3 (2H, d, J= 8.1 Hz), 7.38 (1H, br s), 7.61 (2H, d, J= 8.4 Hz), 9.23 (1H, br s), 9.7 (1H, br s), 10.15 (1H, s).

EXAMPLE 32

Preparation of 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-(4-toluenesulphonylamino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride



2-(4-(4-Toluene sulphonyl amino)phenyl)ethylamine, hydrochloride (0.14g, 0.428 mM) was dissolved in 1 ml of methanol. To the reaction mixture was added, triethyl amine (0.07g) followed by 7-chloro-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.126g, 0.6 mM). Reaction mixture was stirred at room temperature for 48 hrs. The solvent was removed and the residue was purified on a silica gel column using methanol-chloroform system to obtain the amine (0.117g, 54%). It was then converted to its hydrochloride salt using conventional method to obtain the desired compound as a white solid.

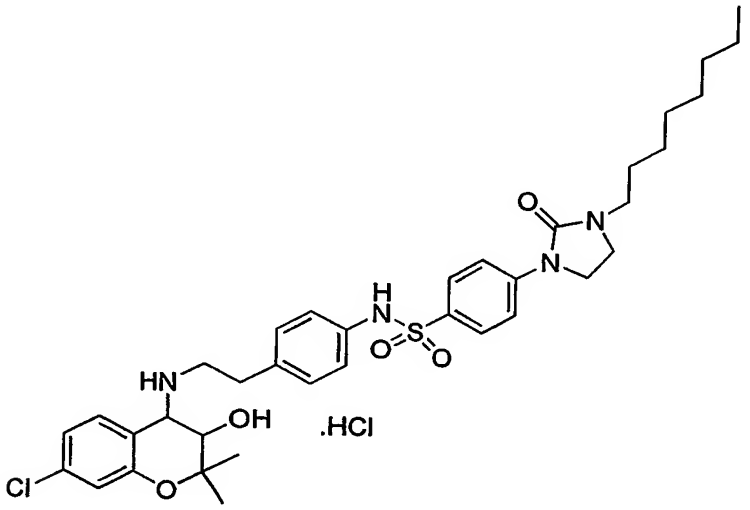
Yield 0.08g (35%), m.p. >200°C.

IR (KBr): 3274, 3052, 1598, 1570, 1489, 1341, 1156, 1093, 1080, 959, 915 cm^{-1}.

NMR (DMSO) δ: 1.04 (3H, s), 1.41 (3H, s), 2.32 (3H, s), 2.8 – 3.2 (4H, m), 3.8-4.0 (1H, m), 4.3-4.5 (1H, m), 6.30 (1H, d, J= 5.5 Hz), 6.94 (1H, d, J = 2.2 Hz), 7.02 (2H, d, J = 8.4 Hz), 7.08 (2H, d, J = 8.4 Hz), 7.33 (2H, d, J = 8.06 Hz), 7.63 (2H, d, J = 8.06 Hz), 7.67-7.7 (1H, m), 9.19 (1H, br s), 9.62 (1H, br s), 10.21 (1H, s).

EXAMPLE 33

Preparation of 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-((4-(3-oct-1-yl)-2-oxo)imidazolidinyl)benzene sulphonyl amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride



To a solution of 2-(4-((4-(3-oct-1-yl)-2-oxo)imidazolidinyl) benzene sulphonyl amino)phenyl)ethylamine, hydrochloride (0.12g, 0.235 mM) in 2 ml of MeOH was added triethyl amine (0.035g) followed by 7-chloro-3,4-dihydro-2,2-dimethyl-3,4-epoxy-2*H*-1-benzopyran (0.059g, 0.28 mM). Reaction mixture was stirred at room temperature for 48 hrs. The solvent was removed and the residue was purified on a silica gel column using methanol-chloroform system to obtain the amine (0.06g). It was then converted to its hydrochloride salt using conventional method to obtain the desired compound as a white solid.

Yield of 0.05g (29%), m.p. 164-166°C.

IR (KBr): 2928, 2855, 1689, 1595, 1484, 1428, 1272, 1158 cm^{-1}.

NMR (CD_3OD) δ: 0.88 (3H, t, J= 6.6 Hz), 1.16 (3H, s), 1.24-1.6 (12 H, m), 1.48 (3H, s), 2.85-3.14 (4 H, m), 3.23 (2H, t, J= 7.2 Hz), 3.5 (2H, t, J= 7.8 Hz), 3.79-3.85 (2H, m), 3.89 (1H, d, J= 9.6 Hz), 4.39 (1H, d, J = 9.9 Hz), 6.84 (1H, dd, J= 2.1 & 8.4 Hz),), 6.87 (1H, d, J= 1.8 Hz), 7.05-7.12 (5H, m), 7.6 (2H, d, J= 9 Hz), 7.67 (2H, d, J= 9.3 Hz).

Pharmacological Experiments

The following pharmacological experiments were performed in order to evaluate the activities of the representative compounds of the present invention in terms of:

1) Radioligand Binding assay for $ß_1$, $ß_2$ and $ß_3$ AR in human recombinant cells.

2) Antidiabetic studies.

3) Behavioural and toxicology studies.

1) Radioligand Binding assay for $ß_1$, $ß_2$ and $ß_3$ AR in human recombinant cells.

First the establishments of the cell lines highly expressing human $ß_1$, $ß_2$ and $ß_3$ adrenergic receptors are explained.

β_1 -AR Binding Studies:

Radioligand binding assay for β_1-AR was carried out in Human recombinant Rex 16 cells. To prepare the membrane, cells were washed twice in 50 mM HEPES (pH 7.5, 4 mM $CaCl_2$, 0.04% BSA, 10% sucrose), harvested and homogenized in HEPES. Homogenate was centrifuged at 30,000 x g for 10 min and pellet was resuspended in HEPES. The final volume of 0.1 mL containing 20 µg of membrane, buffer (50mM Tris-HCl, 5mM EDTA, 1.5mM $CaCl_2$, 120mM NaCl, 1.4mM ascorbic acid, 10mg/l BSA, pH-7.4) [^{125}I] Iodocyanopindolol (30 pM, 2200 Ci/mmol, Amersham) was incubated with varying concentration of competing drugs for 60 min at room temperature. Incubations were stopped by filtering over GF/C (presoaked in 0.5% polyethylenimine) using 96 well Filtermate harvester and washed three times with 2 mL of ice cold 50 mM TRIS-HCl (pH 7.4) containing 4 mM $CaCl_2$.Filters were counted in Packard γ-counter (TOPCOUNT). Nonspecific binding was determined in the presence of S(-)Propranolol (100µM).

β_2 -AR Binding Studies:

Radioligand binding assay for β_2-AR was carried out in Human recombinant CHO-MBR1 cells. To prepare the membrane, cells were washed twice in 50 mM HEPES (pH 7.5, 4 mM $MgCl_2$,0.04% BSA, 10% sucrose), harvested and homogenized in HEPES. Homogenate was centrifuged at 30,000 x g for 10 min and pellet was resuspended in HEPES. The final volume of 0.1 mL containing 20 µg of membrane, buffer (50mM Tris-HCl, 0.5mM EDTA, 5mM $MgCl_2$, 120mM NaCl, 1.4mM ascorbic acid, 10mg/l BSA, pH-7.4), [^{3}H] CGP-12177 (200 pM, 60 Ci/mmol, Amersham) was incubated with varying concentration of competing drugs for 60 min at room temperature. Incubations were stopped by filtering over GF/C (presoaked in 0.5% polyethylenimine) using 96 well Filtermate harvester and washed three times with 2 mL

of ice cold 50 mM Tris-HCl (pH 7.4) containing 4 mM $MgCl_2$. Filters were counted in Packard γ-counter (TOPCOUNT). Nonspecific binding was determined in the presence of ICI- 118551 (10μM).

β-3 AR Binding Studies:

Radioligand binding assay for β_3-AR was carried out in Human recombinant HEK-293 cells. To prepare the membrane, cells were washed twice in 50 mM HEPES (pH 7.5, 4 mM $MgCl_2$,0.04% BSA, 10% sucrose), harvested and homogenized in HEPES. Homogenate was centrifuged at 30,000 x g for 10 min and pellet was resuspended in HEPES. The final volume of 0.1 mL containing 20 μg of membrane, buffer (20mM Tris-HCl, 120mM NaCl, 50mg/L ascorbate, 2mM $MgCl_2$, 4mg/l BSA, pH-7.4),, [^{125}I] Iodocyanopindolol (500 pM, 2200 Ci/mmol, Amersham) was incubated with varying concentration of competing drugs for 60 min at room temperature. Incubations were stopped by filtering over GF/C (presoaked in 0.5% polyethylenimine) using 96 well Filtermate harvester and washed three times with 2 mL of ice cold 50 mM TRIS-HCl (pH 7.4) containing 4 mM MgCl2. Filters were counted in Packard γ-counter (TOPCOUNT). Nonspecific binding was determined in the presence of Alprenolol (1mM).

The primary assay was conducted at one concentration of 10μM and only compounds with significant response were taken for IC_{50} determination. IC_{50} values were calculated from percent inhibition of specific binding at various concentrations using Graphpad software.

The results of Radioligand Binding assays for human recombinant adrenergic $ß_3$ receptors showing percent inhibition of specific activity at 10μM are shown in the Table 1.

The IC_{50} values of the compounds on Human Adrenergic $ß_1$, $ß_2$ and $ß_3$ receptors are shown in Table 2.

TABLE 1

Showing percent inhibition of specific binding of human adrenergic β_3 receptors at 10μM concentration of compounds.

S. No.	Example Number	% Inhibition of Specific Activity
1	1	6
2	2	20
3	3	8
4	4	25
5	5	46
6	6	37
7	7	22
8	8	4
9	9	-6
10	10	55
11	11	-2
12	12	20
13	15	64
14	16	77
15	17	25
16	18	33
17	19	44
18	20	46
19	21	70
20	22	4
21	23	15
22	24	8
23	26	77
24	27	92
25	28	37
26	29	58
27	30	8
28	31	40
29	32	56

TABLE 2

Showing IC_{50} values of GRC compounds on Human Adrenergic β_1, β_2 and β_3 Receptors

Adrenergic Receptors	Example- 21	Example- 26
β_1	36.7 μM	21 μM
β_2	>1000 μM	44.0 μM
β_3	8.55 μM	7.14 μM

2) Antidiabetic Studies.

C57/BL/KSJ- Lep^{db} (db/db) mice of either sex were used. The lean C57/BL/KSJ mice were used as lean control. Both the strains were initially procured from Jacksons Laboratories (USA) and bred successfully at Glenmark Research Centre.

Housing:

All the animals (5mice/cage) were housed in polypropylene cage with free access to water and pellet diet (Nav Bharat Chakan Oil Mills, Chakan). The temperature was maintained at $22\pm1^{0}C$ at the control with a 12:12 hrs light-dark cycle.

Selection & Treatment of animals:

All the experimental procedures were approved by Institutional Animal Ethics Committee. At the beginning of the experiment 10 lean C57/BL/KSJ and 30 C57/BL/KSJ-- Lep^{db} (db/db) mice were obtained. The 0 day serum glucose and triglyceride levels were determined employing glucose (GOD) and triglyceride (GPO-PAP) kits using Vitalab Selectra-2 (E-Merck) Biochemical Analyser. Mice having glucose level of 300-600 mg/dl and triglyceride level of 115 to 135 mg/dl were selected (10 animals/group) for studies.

Compound of Example 26 was prepared freshly in 0.5% carboxy-methyl cellulose (CMC). Control groups of lean and db/db mice received 0.5% CMC and test group received Example 26 and Example 10 (10mg/kg) by oral gavages daily for 14 days at a constant volume of 1ml/kg. At the end of prescribed treatment period animals were bled through retro orbital plexus on 0, 7 and 14 days, one hr after the administration of compound. Serum samples were collected and processed for the measurement of biochemical parameters as mentioned above.

Results:

Compound of Example 26 at daily dose of 10 mg/kg, p.o. exhibited 43% and 51% reduction in serum glucose levels on 7^{th} and 14^{th} day of treatment, respectively that were significantly different as compared to the vehicle control group.

The serum triglyceride levels significantly reduced in Example 26 treated mice on day 7.

Compound of Example 10 at daily dose of 10 mg/kg, p.o. exhibited 23% and 7% reduction in serum glucose levels on 7^{th} and 14^{th} day of treatment, respectively. The serum triglyceride levels reduced in Example 10 treated mice on day 7 while no

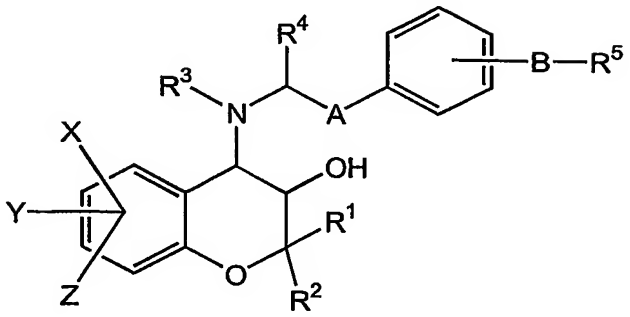
difference was observed on day 14 of treatment between Example 10 treated and vehicle control groups.

3) Behavioural and Toxicity Studies

No behavioral changes were observed in any of the compounds of Example 26, Example 10, Example 17 and Example 32 treated mice up to the maximum dose level of 2000, 2000, 500 and 2000 mg/kg respectively. No changes in gross pathomorphology of vital organs were observed in any group at the end of 14 days of observation.

CLAIMS

1. A compound of the general formula (1)



(1)

wherein X, Y and Z independently may be same or different and represent hydrogen, hydroxy, carboxyl, cyano, amino, nitro, halogen, formyl, oxo (=O), haloalkyl, cycloalkylalkyl, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkynyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclic ring or -COR, -COOR, -C(O)NRR^y, -NRR^y, -NRSO$_2$R^y, -NRS(O)R^y, -OR, -OCOR, -OC(O)R-, -OCONRR^y, -ROR, -RCOOR, -RC(O)NRR^y, -RCOR, -RCS, -SR, -SOR, -SO$_2$R, -SO$_2$NRR^Y, -SONRR^Y (wherein R, R^y or R^z in each of the above groups can be hydrogen, alkyl, aryl, cycloalkyl, arylalkyl, , heterocyclic ring) or

Y and Z together form a 5 to 7 membered saturated, partly unsaturated or aromatic carbocyclic ring or heterocyclic ring having up to 2 hetero atoms selected from the series comprising S, N and O and which are optionally substituted by identical or different substituents selected from the group comprising straight chain or branched alkyl and alkoxy having in each case up to 6 carbon atoms, hydroxyl, cycloalkyl having 3-7 carbon atoms, phenyl, halogen, cyano, oxo (C=O) and nitro;

wherein R^1 and R^2 may independently be the same or different and represent hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted arylalkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted aryl, or R^1 and R^2 together with a carbon atom to which they are attached form a 5-7 membered carbocyclic ring;

wherein R^3 is substituted or unsubstituted alkyl, hydrogen, alkoxycarbonyl, benzyl, or benzyloxycarbonyl;

wherein R^4 is hydrogen, substituted or unsubstituted alkyl, hydroxy alkyl, alkoxyalkyl or haloalkyl, wherein when R^4 is an alkyl group, R^4 and benzene may optionally together with a carbon atom to which they are attached form a carbocyclic ring;

wherein A is $-(CH_2)_n-$, in which n is 0, 1,2 or 3;

wherein B is chemical bond, –O- or $N(R^6)$;

wherein R^6 may be hydrogen , substituted or unsubstituted alkyl, substituted or unsubstituted aryl or substituted or unsubstituted arylalkyl;

wherein R^5 may be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, substituted heterocyclic ring, $-RCOOR^x$, $-SO_2R$, $-CONHSO_2R$, -C(O)NHR, -C(S)NHR, -COOR, -C(O)R, -ROH, $-RCONH_2$, -RCONHOH, $-R(COOH)_2$, $-RSO_3H$;

wherein R and R^x in each of the above groups can be hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl or substituted or unsubstituted heterocyclic ring;

or an analog, a tautomer, a regioisomer, a stereoisomer, a diasteromer, an enantiomer, a geometrical isomer, a polymorph, a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate of the compound of formula (1).

2. 4-Benzylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol . Hydrochloride.

3. 3,4-Dihydro-2,2-dimethyl-4-(2-phenyl)ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride.

4. 3,4-Dihydro-2,2-dimethyl-4-(2-(4-methoxy)phenyl)ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride.

5. 3,4-Dihydro-2,2-dimethyl-4-(2-(4-(3-phenyl)urido)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride.

6. 2-[4-[*N*-Boc-*N*-[-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran yl]aminoethyl]phenoxy] acetic acid ethyl ester.Hydrochloride.

7. 3',4'-Dihydro-3'-hydroxy-4'-(2-(4-methoxy)phenyl)ethylaminospiro [cyclohexane-1,2'-[2*H*]-[1]-benzopyran]. Hydrochloride.

8. 3',4'-Dihydro-3'-hydroxy-4'-(2-phenyl)ethylaminospiro[cyclohexane-1,2'-[2*H*]-[1]-benzopyran].Hydrochloride.

9. 4-[2-[4-Benzyloxyphenyl]-1-hydroxymethyl]ethylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol. Hydrochloride.

10. 3,4-Dihydro-2,2-dimethyl-4-(1-hydroxymethyl-2-phenyl)ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride.

11. 3,4-Dihydro-2,2-dimethyl-4-(2-(4-(4-toluenesulphonylamino))phenyl) ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride.

12. 3,4-Dihydro-2,2-dimethyl-4-[1-methoxymethyl-2-phenyl]ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride.

13. 4-((4-(4-Benzyloxy)phenyl)-2-hydroxy-2-methyl)but-3-ylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol

14. 3,4-Dihydro-2,2-dimethyl-4-(1-methoxymethyl-2-(4-methoxy)phenyl) ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride.

15. 4-[2-[4-benzyloxyphenyl]-1-methoxymethyl]ethylamino-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3-ol.Hydrochloride.

16. 3,4-Dihydro-2,2-Dimethyl-4-(2-(4-(1-pyrrolo)benzenesulphonylamino) phenyl)ethylamino-2*H*-1-benzopyran-3-ol hydrochloride.

17. 3',4'-Dihydro-3'-hydroxy-4'-(2-(4-(4-toluenesulphonylamino))phenyl) ethylaminospiro[cyclohexane-1,2'-[2H]-[1]-benzopyran].Hydrochloride

18. 3,4-Dihydro-2,2-dimethyl-4-(2-(4-(4-methoxy)benzamido)phenyl) ethylamino-2*H*-1-benzopyran-3-ol . Hydrochloride

19. 3,4-Dihydro-2,2-dimethyl-4-(2-(*N*-methyl-4toluenesulphonyl)amino) phenyl)ethyl amino-2*H*-1-benzopyran-3-ol.Hydrochloride

20. 3,4-Dihydro-2,2-Dimethyl-4-(2-(4-(4-nitro)benzenesulphonyl)amino) phenyl)ethylamino-2*H*-1-benzopyran-3-ol.

21. 3',4'-Dihydro-3'-hydroxy-4'-(2-(4-methoxybenzamido)phenyl) ethylaminospiro [cyclohexane-1,2'-[2*H*]-[1]-benzopyran]. Hydrochloride.

22. 6-Chloro-2,2-dimethyl-3,4-dihydro-4-(2-(4-(4-toluenesulphonylamino)) phenyl)ethylamino-2*H*-1-benzopyran-3-ol. Hydrochloride.

23. 3,4-Dihydro-2,2-dimethyl-4-[[3-[4-methoxy]phenyl]prop-2-yl]amino-*2H*-1-benzopyran-3-ol. Hydrochloride.

24. 2-[4-[*N*-[7-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy] acetic acid ethyl ester. Hydrochloride.

25. 2-[4-[*N*-[7-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy] acetic acid.Hydrochloride.

26. 3,4-Dihydro-2,2-dimethyl-4-[2-[4-[4-[3-[hex-1-yl]]urido] benzenesulfonamido]phenyl]ethylamino- 2*H*-1-benzopyran-3,6-diol.

27. 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-(4-fluoro)benzamido)phenyl) ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride.

28. 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-(4-bromo benzene sulphonyl amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.

29. Carbonic acid, phenylmethyl-4-(*N*-(7-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl) aminoethyl)phenyl ester.Hydrochloride.

30. 2-[4-[*N*-[6-Chloro-3,4-dihydro-2,2-dimethyl-3-hydroxy-2*H*-1-benzopyran-4-yl]aminoethyl]phenoxy] acetamide-*N*'-hex-1-yl.Hydrochloride.

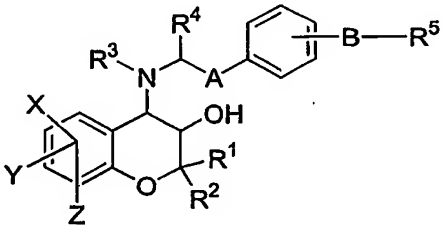
31. 3,4-Dihydro-4-(2-(4-(4-fluoro)benzamido)phenyl)ethylamino)-2*H*-1-benzopyran-3-ol.Hydrochloride.

32. 3,4-Dihydro-2,2-dimethyl-6-methoxy-4-(2-(4-(4-toluene sulphonyl amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride.

33. 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-(4-toluene sulphonyl amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride.

34. 7-Chloro-3,4-dihydro-2,2-dimethyl-4-(2-(4-((4-(3-oct-1-yl)-2-oxo)imidazolidinyl) benzene sulphonyl amino)phenyl)ethylamino-2*H*-1-benzopyran-3-ol.Hydrochloride.

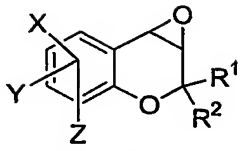
35. A process for the preparation of a compound of the general formula (1)



1

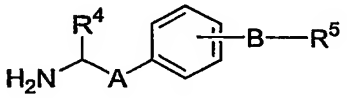
wherein all the symbols have the meanings given in claim 1 which comprises

a) reacting a compound of the general formula (10)



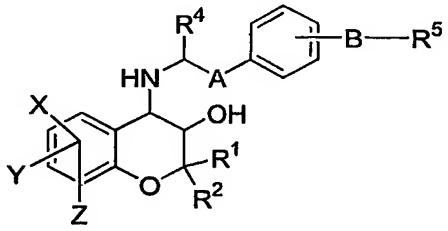
10

wherein all the symbols have the meanings given earlier with a compound of the formula (11) or a salt thereof



11

wherein all the symbols have the meanings given in claim 1 to obtain the compound with general formula (**1a**)



1a

wherein all the symbols have the meanings given above; and

(b) reacting the compounds of the general formula **1a** with the compound of general formula **12**

$$P\text{-}R_3$$

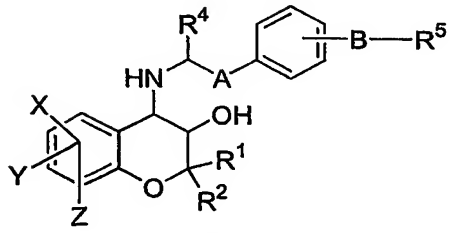
12

where P represents halogen such as Cl or Br and R3 has the meaning given above or P-R_3 is amino protecting reagent to obtain the compound of general formula **1**, and optionally,

(c) converting the compound of the general formula 1 wherein all the symbols have the meanings given above into an analog, a tautomer, a regioisomer, a diasteromer, an enantiomer, a stereoisomer, a geometrical isomer, a polymorph, a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof; and if desired

(d) further purifying the resulting compound.

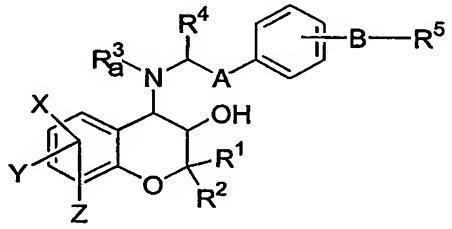
36. A process for the preparation of a compound of the general formula **1a**



(1a)

wherein all symbols have the meanings given for the formula (1) with B = O and wherein R4 is H which comprises:

(a) deprotecting the amino group in the compound of the general formula **(1b)**



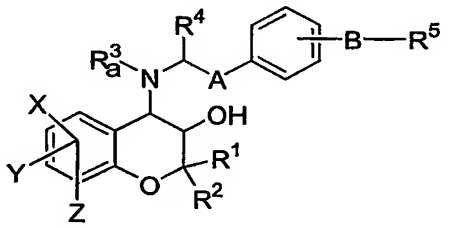
(1b)

wherein R^{3a} represents an amino protecting group all the other symbols have the meanings given in claim1; and optionally

(b) converting the resulting compound of the general formula **(1b)** wherein all the symbols have the meanings given above into an analogs, a tautomer, a regioisomer, a stereoisomer, a diasteromers, a enantiomers, a geometrical isomer, a polymorph, a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof; and optionally

(c) purifying the resulting compound.

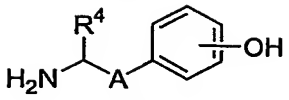
37. A process for the preparation of compounds of formula **(1b)** thereof



(1b)

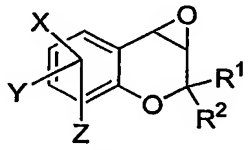
wherein all the symbols have the meanings given in claim **36**, which comprises:

a) reacting a compound of the general formula **13** or a salt thereof



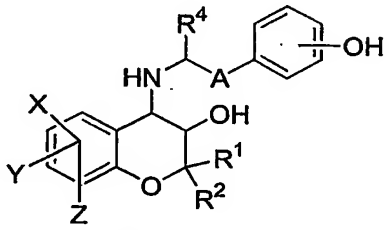
13

with a compound of the general formula **10**



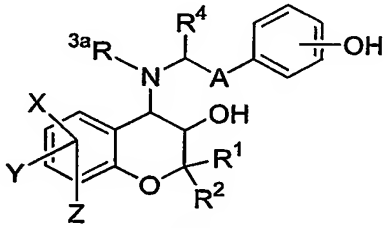
10

where all the symbols have the meanings given in claim 1 and 36 to obtain the compounds of the general formula **14**



14

b) protecting the amino group present in the compound of the general formula **14** to obtain the compound with formula **14a**



14a

where R^{3a} is an amino protecting group and all the other symbols have the meanings given in claim 1 and 36

c) reacting the resulting protected compound of the general formula **14a** with a compounds of the general formula **15**

$$Q\text{-}R^7$$

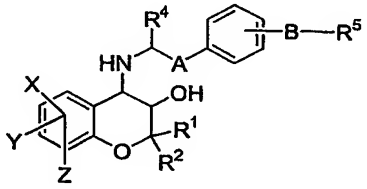
15

where Q represents halogens, sulphonylchloride, isocynate, isothiocyanate, sulphonyl isocyanate, acid chlorides, anhydrides and and R^7 is substituted or unsubstituted alkyl, substituted or unsubstituted aryl, substituted or unsubstituted arylalkyl, sub or unsubstituted alkylaryl, sub or unsubstituted heterocycle,

d) converting the resulting compound of the general formula 1c wherein all the symbols have the meanings given above into an analog, a tautomer, a regioisomer, a stereoisomer, a enantiomer, a diasteromer, a geometrical isomer, a polymorph, a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate thereof; and optionally

e) purifying the resulting compound.

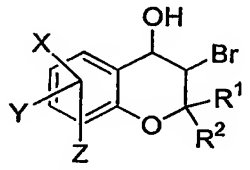
38. A process for the preparation of a compound of general formula **1a** or a salt thereof



[1a]

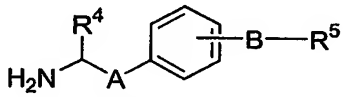
wherein all the symbols have the meanings given earlier which comprises:

a) reacting a compound of the general formula **16**



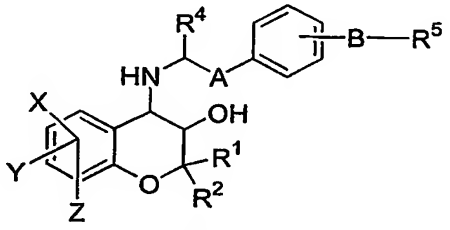
16

where all the symbols have the meanings given in claim 1, with a compound of the general formula **11** or a salt thereof



11

to obtain the compound of the general formula **1a**



1a

and optionally

b) converting the resulting compound of the general formula **1a** wherein all the symbols have the meanings given in claim 1 into an analog, a tautomer, a regioisomer, a stereoisomer, a geometrical isomer, a polymorph, a pharmaceutically acceptable salt, or a pharmaceutically acceptable solvate; and optionally

c) purifying the resulting compounds by conventional methods.

39. A pharmaceutical composition for use as beta 3 adrenoceptor agonist comprising the compounds of claim 1 and a pharmaceutically acceptable carrier or excipient.

40. A pharmaceutical composition as claimed in claim 39, comprising one or more clinically useful anti diabetic agents.

41. A pharmaceutical composition as claimed in claim 39 or 40, wherein the composition is in the form of a capsule, a tablet, a powder, a syrup, a solution, or a dispersion.

42. A method for stimulating metabolic activity in a patient to be treated comprising administering to the patient the compound of formula (1) in an amount effective for such stimulation.

43. A method for increasing sensitivity of a patient to insulin comprising administering to the patient the compound of formula (1) in an amount effective to increase such sensitivity.

44. The compound of formula (1) for use in therapy.

45. Use of a compound of formula (1) for the manufacture of a medicament for therapeutic application in lowering serum glucose and triglyceride levels.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/23884

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 C07D311/68 A61K31/35 A61K31/40 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 412 531 A (KAKEN PHARMA CO LTD) 13 February 1991 (1991-02-13) Compounds II; ex. 9 (p. 15, 30-31) ---	1
X	NICOLAOU ET AL.: "Natural Product-like Combinatorial Libraries Based on Privileged Structures. 3. The "Libraries from Libraries" Principle for Diversity Enhancement of Benzopyran Libraries" J. AM. CHEM. SOC., vol. 122, 2000, pages 9968-9976, XP002214994 Compound 23, entry 19 table 2 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 October 2002	15/10/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fritz, M

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/23884

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CONNORS ET AL.: "The Synthesis and Potassium Channel Blocking Activity of Some (4-Methanesulfonamidophenoxy)propanolamine s as Potential Class III Antiarrhythmic Agents" J. MED. CHEM., vol. 34, 1991, pages 1570-1577, XP002214995 Compound 17b page 1572	1
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